DOCTOR OF PHILOSOPHY

Evaluation and management of hospital antibiotic use

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Faranak Ansari

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For the degree of Doctor of Philosophy

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Dedication

To the loving memory of my father

To my husband and my daughter: Hossein and Mehregan

To my mother

To my brother and sisters

Farrokh, Fariba and Farzaneh

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1. Ansari, F., Molana, H., Goossens, H., Davey, P. Changes in antibacterial use in hospitals from 18 European countries: the European Surveillance of Antimicrobial Consumption (ESAC) longitudinal survey 2000 to 2006. Accepted for publication. J Antimicrob Chemother.
2. Ansari, F., Erntell, M., Goossens, H., Davey, P. The European surveillance of antimicrobial consumption (ESAC) Point-prevalence survey of antibacterial use in 20 European hospitals in 2006. Clin Infect Dis. 2009 Nov 15;49(10):1496-504.
3. Ansari, F., Gray, K., Nathwani, D., Phillip, G., Ogston, S., Ramsay, C., Davey, P. Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. J of Antimicrobial Chemotherapy. 2003, 52: 842-48. Cited 51 times.

Conference presentations

1. Muller, A., Coenen, S., Ansari, F., Vankerckhoven, V., Hendrickx, E., De Smet H., Goossens, H., and the ESAC Project Group European Surveillance of Antimicrobial Consumption (ESAC). 18th ECCMID Congress, April 2008, Barcelona, Spain.
2. Erntell, M., Ansari, F., Goossens. H., Davey, P., for the ESAC II HC Subproject Working Group. ESAC II Hospital Care Subproject 2005-2007: patterns of antibiotic use in relation to diagnoses in 19 European hospitals in 2006, Point Prevalence Study, ECCMID Congress, March 2007, Munich, Germany
3. Ansari, F., Goossens, H., Davey, P., on behalf of the ESAC II HC Subproject Working Group ESAC II Hospital Care Subproject 2005-2007. Improving quality indicators of hospitals antibiotic prescribing within standardised data, Longitudinal Study. ECCMID Congress, March 2007, Munich, Germany.
4. Ansari, F., Goossens, H., Davey, P. The ESAC II Hospital Care Subproject: developing indicators for antibiotic consumption surveillance. Invited speaker. National Symposium on "Improving Antibiotic prescribing and new approaches". May 2006, Brussels, Belgium
5. Ansari, F., Scahill, L., Davey, P. Improving Quality Indicators for Hospital Antibiotic Prescribing: using simple data and easy tool. FIS Conference. November 2006, Cardiff, UK.
6. Ansari, F., Scahill, L., Nathwani, D., Davey, P. Indicators of Hospital Antibiotic Prescribing. BSAC and APUA meeting “Resistance to change: strategies to improve antimicrobial use”. October 2006, London, UK
7. Ansari, F., Scahill, L., Nathwani, D., Davey, P. Management of Antibiotic Prescribing in the Tayside Acute Services Division (ASD), NHS Tayside. Euro-DURG Ulster meeting, June 2005, Coleraine, Northern Ireland, UK

8. Ansari, F., Scahill, L., Gray, K. Nathwani, D., Davey, P. Management of Antibiotic Prescribing in Tayside University Hospitals. Adverse Incident Pester Competition, NHS Tayside. June 2005. Dundee, UK.
9. Ansari, F., Scahill, L., Nathwani, D., Davey, P. Utilisation Review of Antibiotic Prescribing in Tayside University Hospitals'- SSHAIPing the Future of HAI, November 2004. Dunblane, UK.
10. Ansari, F., Gray, K., Nathwani, D., Phillips, G., Ogston, S., Ramsay, C., Davey, P. Outcomes of an Intervention to Improve Hospital Antibiotic Prescribing: Interrupted Time Series analysis with Segmented Regression. ISPOR Congress, November 2003, Barcelona, Spain.
11. Ansari, F., Gray, K., Nathwani, D., Phillips, G., Ogston, S., Ramsay, C., Davey, P. Evaluation of outcomes of Alert Antibiotics Monitoring in Tayside university hospital: interrupted time series analysis. FIS conference, November 2002, Manchester, UK.

List of Abbreviations

AB	Antibacterial
ACF	Autocorrelation function
AD	Admissions
ADF	Augmented Dickey-Fuller
AIC	Akaike information criterion
AMG	Antimicrobial management group
AR	Autoregressive
ARIMA	Autoregressive integrated moving average
ARMA	Autoregressive moving average
ARPAC	Antimicrobial resistance: prevention and control
ASD	Acute services division
ATC	Anatomic , therapeutic, chemical classification
B-G LM	Breusch-Godfrey Lagrange Multiplier
CAI	Community acquired infection
CAP	Community acquired pneumonia
C difficile	Clostridium difficile
CI	Confidence intervals
CQ	Third generation Cephalosporins and Fluoroquinolones
CV	Coefficient of variation
DAD	DDD per 100 admissions
DBD	DDD per 100 bed-days
DDD	Defined daily dose
DU90%	Drugs accounted for 90% of total use
DU75%	Drugs accounted for 75% of total use
DUR	Drug utilisation research

DW	Durbin-Watson
ECCMID	European Congress of Clinical Microbiology and Infectious Diseases
E-Coli	Escherichia coli
EARSS	European antimicrobial resistance scheme
ESAC	European surveillance of antimicrobial consumption
ESAC-HC	ESAC- hospital care subproject
EU	European Union
FTE	Full time employee
HAI	Health care associated infection
ICC	Infection control committee
ICU	Intensive care unit
ID	Infectious diseases
IQR	Inter-quartile range
ITS	Interrupted time series
ITSA	Interrupted time series analysis
KPPS	Kwiatkowski-Phillips-Schmidt-Shin
LOS	Length of hospital stay
LS	Longitudinal survey
MA	Moving average
MRSA	Methicillin-resistant Staphylococcus aureus
OBD	Occupied bed days
OR	Odds ratio
PAC	Partial autocorrelation function
PDD	Prescribed daily dose
PP	Phillips- Perron
PPS	Point prevalence survey
SAPG	Scottish antimicrobial management group

SBC	Schwartz Bayesian Criterion
SSTBJ	Skin, soft tissue, bone and joint
STRAMA	Swedish strategic programme for rational use of antimicrobial agents and surveillance of resistance
TSA	Time series analysis
WHO	World health organisation

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My acknowledgements also go to Ms Hazel Braid at DHSRU for proofreading this thesis.

Declaration

I declare that my thesis “Evaluation and Management of Hospital Antibiotic use” has been has been composed by myself and that the research it describes has been done by me. I am the sole author of this. I have consulted all the references cited. This research has not been previously submitted for higher degree. Any element of joint work with others has been clearly defined.

Signature

Faranak Ansari

Date October 2010

Certificate

I certify that Faranak Ansari has completed the equivalent of nine terms of experimental research and that she has fulfilled the conditions of the relevant Ordinance and Regulations of the University of Dundee, so that she is qualified to submit this thesis in application for the degree of Doctor of Philosophy.

Summary

Antimicrobials are unique drugs in that they target “infectious” or “transferable” diseases. There is considerable evidence linking increasing antimicrobial use with increasing resistance. Resistant bacteria do not know the boundaries, either between countries or within a society between hospital and primary care. Inappropriate prescribing of antimicrobials in hospitals therefore has consequences for whole communities and problems may spread both nationally and internationally. The gathering of reliable measurements of antibiotic use in hospitals employing standardised methods is essential to building an evidence base and highlighting inconsistencies at national and international levels.

In this study, after data processing, validating and record linkage, a method for electronic conversion of drug supply data to the ATC/DDD classification and for longitudinal analysis was established for Tayside and then for a set of European hospitals. Time series analysis and interrupted time series analysis were described and used for longitudinal surveillance and interventional study of antimicrobial use. This thesis explores issues concerning the evolution and management of hospital antimicrobial use using a wide range of methods. A series of drug utilisation research studies were implemented as the basis of research methods that, in combination of previously described methods, provided novel studies.

No single measure can currently capture all of the aspects of hospital antibiotic use. However, a combination of detailed, point prevalence data from individual patients with longitudinal analysis of total consumption can provide meaningful data for comparison between hospitals and for analysis of the relationship between use and outcome.

Additionally, there is a need to apply standard processes and novel methods to produce more meaningful surveillances.

Longitudinal and point prevalence surveillances together with an explanation of variations in hospital characteristics are used to produce a set of coherent measurements of hospital antimicrobial use.

Administrative data for longitudinal surveys requires continuous quality control. Whereas drug utilisation researchers and clinicians should target a set of indicators for interventional studies, large studies at national or international level need central data processing by country to identify targets for evaluation and for interventional studies. Support from experts in other fields is needed to address any shortcomings that may be experienced during continuous antibiotic drug utilisation monitoring at national and international levels.

CHAPTER ONE: LITERATURE REVIEW ON MEASUREMENT OF ANTIBIOTIC USE IN HOSPITALS

1.1. Drug Utilisation Research

Drug utilisation research has expanded from simple quantification of drug use by different providers or users of healthcare to include social, economic and qualitative methods with a more generalised public health focus.[1] Drug utilisation was defined by the World Health Organisation (WHO) as "marketing, distribution, prescribing and use of drugs in society with special concern on the resulting medical, social and economic consequences". In this and other definitions of drug utilisation, the non-pharmacologic (socio-anthropological, behavioural, and economic) factors influencing drug utilisation are explicitly or implicitly recognised.[2]

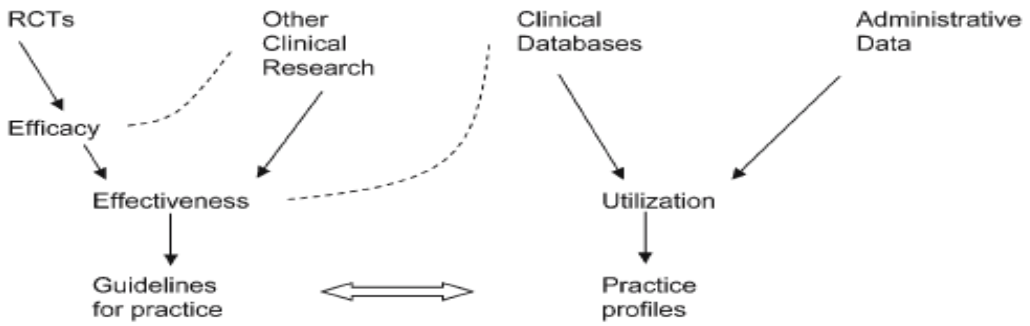
However the definition by WHO goes beyond the process aspects of drug utilisation. Rather, it explores the movement of drugs along other therapeutic drug chains and includes consideration of the outcomes of drug use. According to this definition, studies of drug utilisation include not only studies of medical and non-medical aspects influencing drug utilisation, but also the effects of drug utilisation at all levels. Studies of how drug utilisation relates to the effects of drug use, beneficial or adverse, are usually labelled analytical pharmacoepidemiology research because they apply the classical epidemiological methods for observational or interventional studies of disease aetiology.[2] Drug utilisation research and pharmacoepidemiology have developed along parallel lines, but may now be regarded as interrelated and part of a continuum of interests and methodologies. As stated by Lunde and Baskaas, the general objectives of drug utilisation studies are: "problem identification and problem analysis in relation to importance, causes, and consequences; establishment of weighted basis on problem

solution; and assessment of the effects of the action taken".[3] Drug utilisation may be quantitative or qualitative. The objectives of quantitative drug utilisation studies are to quantify the past and present trends in drug use at various levels whether national, local of reported adverse drug reactions, to monitor use of specific therapeutic classes and to evaluate interventions. Qualitative studies, on the other hand, assess knowledge, skills attitudes or behaviours of prescribers or users of antimicrobials.[2]

In the United States drug utilisation programs are commonly called Drug Use Evaluation (DUE) and they are part of quality assurance activities required by Medicare regulations, the Joint Commission and Accreditation of Health Care Organizations (JCAHO). In Europe, most drug utilisation programs have taken the form of a therapeutic audit performed at various levels (such as patient, prescriber, hospital, county, and national levels) assessing not only clinical consequences but also social and economic consequences.[2] A widely adopted measure of drug utilisation is the number of drugs that account for 90% of total drug use or DU 90% and the percentage of these drugs that adhered to guidelines. [4] Besides being an indicator of the quality of drug use , the DU90%, is a powerful alert and driving force for change.[5]

Measurement of utilisation is an essential component in building the evidence for evaluating health care (Figure 1.1)

Figure 1.1: Building evidence for evaluating health care [6]



Clinical research using Randomised Clinical Trials (RCTs) and other methods establishes the efficacy, safety and overall effectiveness of drugs and other interventions at the individual patient level. Health care utilisation studies derived from administrative and clinical databases establish actual clinical practice profiles and this evidence is used to inform and improve clinical guidelines. [6] Utilisation studies provide essential additional evidence about effectiveness because in addition to efficacy or safety they measure reach, adoption, implementation and maintenance (RE-AIM). The RE-AIM framework for evidence about effectiveness was originally applied to health promotion interventions. [7] However, the same criteria can be applied to quality improvement (Table 1.1).

Table 1.1: RE-AIM criteria for evaluating the impact of an intervention in real life. [7, 8] The RE-AIM model proposes that intervention impact = reach x efficacy, filtered through the organisational dimensions of adoption, implementation and maintenance.

Reach	What proportion of the target population actually get the intervention?
Efficacy	What is the success rate if implemented as in protocol?
Adoption	What proportion of target hospitals/practices/clinicians adopt it?
Implementation	To what extent is the intervention implemented as intended/per protocol?
Maintenance	To what extent is the program sustained over time?

According to the RE-AIM model clinical effectiveness at the individual patient level is not the only dimension that matters if you are deciding whether to use an intervention in a population, because an intervention can be effective in a trial, but ineffective in real-

life implementation. An example of this in pharmaceutical research is the use of COX-2 non-steroidal anti-inflammatory drugs.[8] To quote Guthrie and Wyke: *"According to trials which compared them to older NSAIDs, they have fewer gastric adverse effects, so their introduction was expected to reduce hospital admissions with gastro-intestinal (GI) bleeding because they would be used to substitute for existing NSAID use. Instead, the introduction of 'safer' COX-2 inhibitors in Canada was associated with increased hospital admissions for GI bleeding, because rather than substituting for NSAID prescription, much COX-2 prescription was to patients who would not otherwise have received an NSAID. Implementation therefore served to increase the number of patients exposed to drugs with GI toxicity."* [8]

1.2 Why is the Evaluation of Antimicrobial Use in Hospitals Important?

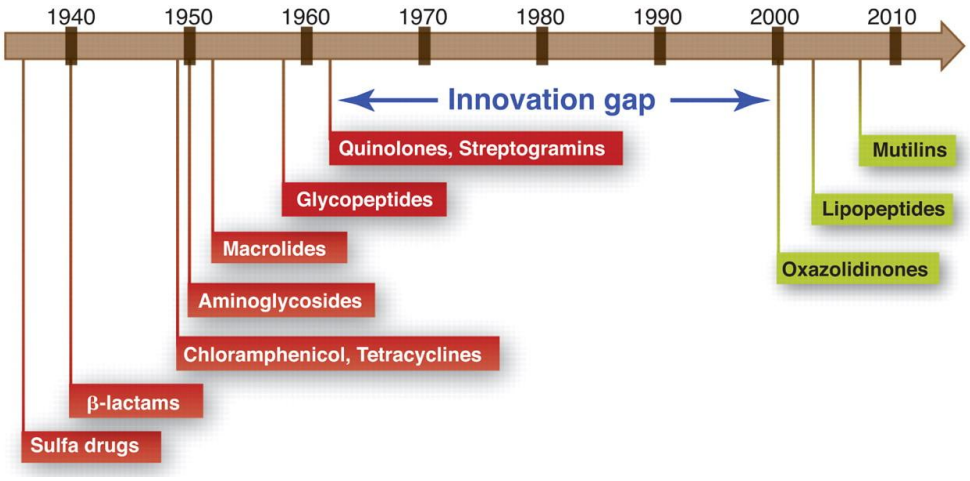
The aim of this section is to review the evidence about consequences of antimicrobial prescribing such as resistance, its relationship with antimicrobial use, patient safety, and attributable costs. Problem areas, deficiencies or controversies relating to the existing knowledge of the topic are identified.

1.2.1 Antibiotics, Past and Present

The development and use of antimicrobial agents was one of the most important measures leading to the control of bacterial disease in the 20th century. Further to improvements in better health and nutrition in general, antibiotics have saved countless lives and transformed the practice of medicine since the first flowering of antimicrobial chemotherapy in the 1930s and 40s. Antimicrobial resistance became a challenge shortly after penicillin gained extensive use in the 1940s, when it was introduced for the treatment of severe staphylococcal infections. In 1947 physicians observed the first

case of clinical resistance and the optimism generated by the dawn of the antimicrobial era was quenched by the emergence of penicillin-resistant *Staphylococcus aureus.* By 1952 75% of *Staph aureus* isolates in hospitals were resistant to penicillin.[9-11] Antimicrobial resistance has become one of the biggest public health issues to be faced at the beginning of the new millennium, with the emergence of a 'post-antibiotic' era threatening current and future medical advances.[12, 13] Moreover, 70 years after introducing antibiotics, mortality as a result of infectious diseases represents one-fifth of global deaths resulting in more than 11 million deaths annually. Respiratory infections are the leading killer, causing nearly four million deaths annually.[14] We are increasingly faced with pathogens for which no effective antimicrobials exist and consequently there is a rise in treatment failure rate. Furthermore, fewer antimicrobial agents are under development. In the past, pharmaceutical industry research efforts always provided clinicians with new and effective alternative agents.[13] Now it may take 10 years to develop a new antimicrobial. Figure 1.2 shows the innovation gap in antibiotic discovery. Between 1962 and 2000, no major classes of antibiotics were introduced.[15] In the developed world, clinicians and scientists are concerned about the slow process of introducing new antibiotics. The Pharmaceutical Industry is mainly concerned with investing time developing drugs to combat chronic diseases rather than drugs such as antibiotics where, with the exception of tuberculosis, the duration of therapy may last only 5 to 7 days.[16, 17]

Figure 1.2: The History of Antibiotic Innovation[15]



1.2.2 Inappropriate Use of Antimicrobials

The World Health Organisation (WHO) estimated that antibiotics account for 15 to 30% of drug expenditures, the largest share of any single drug group.[18, 19] Nevertheless, about half of antibiotic usage in the developed world (and perhaps more in the developing countries) is inappropriate.[20] WHO defines the appropriate use of antibiotics as "the cost-effective use of antimicrobials, which maximises clinical therapeutic effect while minimising both drug-related toxicity and the development of antimicrobial resistance".[21] Globally, there is an extensive overuse of antimicrobials, e.g. use based on incorrect medical indications as well as misuse by using the wrong agent, administration route and dosage or treatment duration.[22, 23] In England general practitioners (GPs, or family doctors) prescribe 270 million antibiotic Defined Daily Doses (DDD) each year. This equates to enough antimicrobials to treat each man, woman and child in England for five days a year.[24]

Between 25% and 50% of hospitalised patients receive antimicrobials, which in turn, account for one-third of the pharmacy budgets of most inpatient facilities and are the leading drug classes causing adverse drug effects with regard to the risk of collateral damage to patient. Furthermore, surveys suggest that these agents are inappropriately

or incorrectly used in 22% to 65% of those treated.[25, 26] Antimicrobials are the largest single group of drugs used in UK hospitals and control of expenditure on them must form a major part of any attempts at pharmaceutical budgeting.[27] As a result attempts to control antimicrobial prescribing in hospitals have examined both acquisition costs and quality of use. However, control of antibiotic use in hospitals is arguably more important for preventing proliferation of multiply resistant organisms than control of community consumption.[27, 28]

Wrong dose, duration and indication

Traditionally, standard antimicrobial regimens for common infections, such as acute Upper Respiratory Tract Infections (URTI), have been administered for duration of 7 to 10 days.[29] There is new accumulating evidence that for single pathogen infections, such as those causing URTI [30], Community Acquired Pneumonia (CAP)[31, 32], otitis media, sinusitis, tonsillopharingitis[29], cystitis[33], and Ventilator Associated Pneumonia (VAP) [34] shortened courses of therapy may be as or more effective than conventional regimens of longer duration. [35-37] Stuart Levy, President of the Alliance for the Prudent Use of Antimicrobials said:*"The number of bacteria resistant to many different antimicrobials has increased, in many cases, tenfold or more. Even new drugs that have been approved are confronting resistance, fortunately in small amounts, but we have to be careful how they're used. If used for extended periods of time, they too risk becoming ineffective early on."* [38] Finally, underuse, through lack of access to effective antimicrobials may also play an important a role in driving resistance as overuse.[21]

Societal barriers

Inappropriate use of antimicrobials is not limited to primary and secondary care or prescribing habits. It is also a societal issue because of public attitudes and beliefs, for

example in their perception of antimicrobials as magic bullets, combined with failure of some governments to regulate antimicrobial sales without prescriptions. In 2001, a large questionnaire study (5,379 subjects) in nine countries indicated that antimicrobials could be obtained without prescription in all countries.[39] Recent surveys indicates obtaining antimicrobials without prescription ranges from 100% of community pharmacies in Athens,[40] 85% in Malta[41] , 80% in Catalonia [42] to 4.8% in UK.[43]

1.2.3. Mechanisms of association between antimicrobial use and resistance

Many bacterial genes responsible for resistance were found in nature before the introduction of antimicrobials. Extensive use of antimicrobial agents benefits the resistant strains or species by eliminating more susceptible competitors.[9] Antimicrobials affect both pathogens and normal flora. The normal flora of the skin and mucous membranes has important protective properties, but it may also serve as a reservoir for resistance. All antimicrobials can be selected for resistance. However, in general, broad-spectrum antimicrobials are more likely to lead to super infections with resistant bacteria than narrow–spectrum antimicrobials because they have an increased potential to interfere with the normal flora. One micro-organism may select resistance to one or more other antimicrobials, because resistance may be genetically linked (co-selection). Therefore, there is an established but complex relationship between consumption of antimicrobials and the prevalence of drug resistant bacteria.[44-48]

The selection of drug-resistant organisms and the unwanted development and colonisation of multidrug-resistant organisms; namely, collateral damage is a term used to refer to the ecologically adverse effects of antimicrobial therapy. The risk of collateral damage induced by different antimicrobial classes can be assessed by a variety of epidemiologic studies. Cephalosporin use has been linked to subsequent infection with vancomycin-resistant enterococci, extended-spectrum β-lactamase–

producing *Klebsiella pneumonia,* β-lactam–resistant *Acinetobacter* species, and *Clostridium difficile.* Quinolone use has been linked to infections with Methicillin-Resistant S*taphylococcus Aureus* (MRSA) and with increasing Quinolone resistance in gram-negative bacilli, such as *Pseudomonas aeruginosa.* Neither third-generation Cephalosporins nor Quinolones appear suitable for sustained use in hospitals as "workhorse" antimicrobial therapies.[49] Data that links information about prescribing and resistance at the population level is subject to ecological bias, which is likely to underestimate the impact of antimicrobial use.[50] There is relatively little information about attributable risk in hospitals because of the scarcity of data about prescribing to individual patients and the difficulty of separating the impact of prescribing from transmission.[51] The best evidence about absolute risk comes from prospective studies that compare patients who do and do not receive antimicrobials. [52]

Mathematical models of the relationship between antimicrobial consumption in human communities and the frequency of resistance suggest that the impact of reduction in prescribing may be critically dependent on the fitness cost of resistance to bacteria.[13, 53, 54] Evidence suggests that antimicrobial resistance is more likely to be encouraged by prolonged courses of low dose treatment rather than by shorter courses at high dose.[55, 56] This theory is supported by mathematical modelling which indicates that the time scale for the emergence of resistance is shorter than the decay time following a decline in antimicrobial consumption and so, as a consequence, the therapeutic goal should be to maximise patient outcome whilst minimising the potential for the selection and spread of resistance. It has been suggested that the best way to achieve this is through the use of agents that elicit rapid eradication of the bacterial population including emerging resistant mutants from the site of infection.[57]

1.2.4 Surveillance of antimicrobial resistance

The European SENTRY Antimicrobial Surveillance Programme analysed the prevalence of resistance to Aminoglycosides in 20 European hospitals in 1998 and reported considerable intra-country variations in the prevalence of resistance phenotypes, Aminoglycoside resistance rates were generally higher in Italy, Portugal, Spain, Greece, France, the UK, and Poland than in Austria, Belgium, Germany, the Netherlands, and Switzerland. Compared with the 1987-88 data of the European Study Group on Antimicrobial Resistance, Gentamicin resistance has increased up to 5% in some gram-negative bacteria species. Furthermore, a greater than 10% increase in resistance to Gentamicin has been seen in *Staphylococcus aureus* during previous decade. The reason for this observation was unclear, although changes in antimicrobial prescribing patterns resulted in increased selective pressure from Gentamicin may have contributed. [58]

In the UK, resistance to the Aminoglycosides, Penicillins and Ceftazidime was significantly higher in 1993 than 1982.[59] The use of βeta-lactams and Macrolides in 1997 and the proportion of resistant isolates of Streptococcus pneumonia to these drugs in 1998 and 1999 were higher in the UK than in Sweden, Netherlands, and Germany and Finland.[60] In Scotland in 2001, the proportion of all *Staphylococcus aureus* isolates due to MRSA was similar to 2000 (40%). During the same period there appeared to be a general increase in the level of resistance to most antimicrobials amongst *E.coli* isolates.[61] The European Antimicrobial Resistance Surveillance Scheme (EARSS) collects routinely generated antimicrobial susceptibility data from 33 European countries.[62] Collective data from community and hospital from 2008 compared with year 2005 show some significant decreases in resistance of *Strep pneumoniae* and *Staph aureus* balanced by alarming increase in resistance of *E coli* and *K pneumonia*.

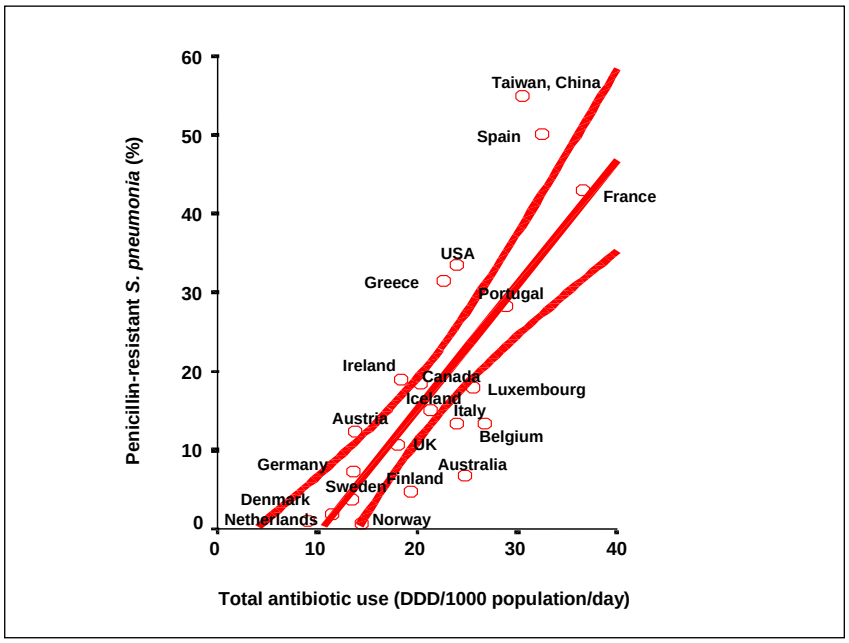
Although multiple resistance of these pathogens to third generation Cephalosporins, Fluoroquinolones and Aminoglycosides is still low (1%) in some countries, resistance to Fluoroquinolones is increasing rapidly and is now >5% in all participating European countries.[52 63]

1.2.5 Evidence linking bacterial resistance with antimicrobial use

Several studies document the effect of change in prescribing on antimicrobial resistance rates. In Japan between 1974 and 1975, a high frequency of Erythromycin resistance (61.8%) was detected among group A streptococcal isolates. The consumption of Macrolides had risen dramatically from 1970 to 1977 and had decreased again by 1984. Between 1981 and 1982, rates of resistance had decreased to about 22%, and after 1983 they remained at between 1 to 3 percent.[9] A seven-year survey (1980-1986) in France showed significant correlation between an increase in antimicrobial use and a decrease in antimicrobial susceptibility, especially for third generation Cephalosporins.[64] In Greece an 80% reduction in Quinolone use was associated with a significant decrease in resistance amongst gram-negative bacilli.[65] In the Netherlands increased resistance of pneumococci to Erythromycin followed an increase in the use of Macrolides with a time lag of 2 to 3 years.[66] In Finland, after a nationwide significant reduction of 57% use of Macrolides in 1992 compared with 1991 and steady low use until 1997, the frequency of Erythromycin resistance among group A streptococcus isolates significantly changed from 16.5% in 1992 to 8.6% in 1996.[67] Surveillance of AMR using the European Antimicrobial Resistance Surveillance System (EARSS) and antibacterial sales data from 11 European countries showed a linear relationship between the use of βeta-lactam antimicrobials and Macrolides in 1997 and the proportion of *Penicillin-Nonsusceptible Streptococcus pneumonia* (PNSP) in 1998-1999.[68] This association between antimicrobial use and resistances is also seen on a larger scale, as the frequency of

resistant bacteria is considerably higher in countries with high antimicrobial consumption. If total outpatient antimicrobial consumption in different countries is correlated with the rate of penicillin-resistant *Streptococcus pneumonia* (PRSP) , then a direct correlation is seen (Spearman coefficient r = 0.75; $P < 0.001$) (Figure 1.2).[69]

Figure 1.3: Correlation between penicillin-resistant (non-susceptible) pneumococci and outpatient antibiotic use (with 95% confidence intervals) [69]



Studies in primary care with patient level data show that prior Trimethoprim use is associated with increased risk of infection with *E.coli* resistant either to Trimethoprim or to other antibacterials within 0-12 months. [50, 70-72] Studies of the incidence of colonisation with drug resistant bacteria provide particularly convincing evidence of a time sequence consistent with the selection of drug-resistant bacteria through exposure to antimicrobials. [71] The departmental consumption of Cephalosporins and Amikacin in six autonomous departments of medicine in a Dutch hospital in the year before was associated with a measurable and statistically significant increase in the probability of

infection caused by a resistant pathogen.[51] There is further evidence that spread of antimicrobial resistance in hospitals and in community is driven by increased use of antimicrobials.[73-75]

However, it does not follow that reversal of resistance will follow decrease use.[76] A recent prospective interventional study in Sweden found despite 85% reduction in use of Trimethoprim containing antibacterials, 2 years after the intervention there was a marginal but significant increase in resistant E.coli isolates both in primary care and in hospital. The authors reported that no change in trimethoprim resistance occurred after a large reduction in trimethoprim use.[77] A UK study provided evidence that despite huge decrease in human sulphonamide use during 1991-1999, Sulphamethoxazole resistant *E coli* isolates remained equally high in 1999 versus 1991. Resistance to six of eight other antimicrobial agents tested was significantly more frequent ($P<0.05$) in sulphonamide-resistant than sulphonamide-susceptible isolates in both 1991 and 1999.[78] There are two likely explanations for these results. First sulphamethoxazole and trimethoprim resistance is linked to other mechanisms of resistance so other antibacterials will exert selective pressure for this gene to be conserved.[76, 77] Second sulphamethoxazole and trimethoprim resistance have been well established for decades and are not associated with much fitness cost for the bacteria.[77] In contrast, quinolone resistance in *E coli* has emerged relatively recently and is associated with considerable fitness cost.[79] Consequently, national restriction of ciprofloxacin in Israel was associated with rapid decrease in resistance in *E coli*, which returned to previous levels after the restriction was lifted.[80]

In conclusion, there is considerable evidence linking increasing antimicrobial use with increasing resistance. Although it does not follow that reducing use will result in reversal of resistance, this is more likely to occur in hospitals than in the community

and can occur in the community provided that acquisition of resistance is still associated with some fitness cost for the bacteria.

1.2.6 Special concerns about hospital antimicrobial use

Antimicrobial resistant pathogens are increasingly common causes of health care associated infections (HAI) and are resulting in prolonged hospital stays, increased antimicrobial use, increased morbidity and mortality, greater direct and indirect costs, and greater opportunities for the spread of infection to other individuals.[26, 81] Much antimicrobial prescribing is likely to be of limited therapeutic value and there is some evidence that lower rates of antimicrobial prescribing may also lead to lower rates of antimicrobial resistance.[82] About nine patients in every 100 admitted to hospital in Scotland acquire an infection during their hospital stay.[83] In 20 teaching and non-teaching hospitals in the UK, types of MRSA had an 11% increase rate in two consecutive years starting from 1996.[60] Several studies have observed increased mortality in VAP caused by multiply resistant bacteria compared with other bacterial pathogens, which they have attributed to a higher risk of initial inappropriate antimicrobial therapy in these patients.[84-88] However, Schwaber and Carmelli have questioned the reliability of the measurement of appropriateness in these studies. [89] Zervos et al. in a 10 year survey (1991-2000) on use of and resistance to Fluoroquinolones in 10 US hospitals found that increase in resistance was associated with increased use and the changes were hospital specific.[90] In a London hospital, the increase and decline in the frequency of Erythromycin resistance among *Staphylococcus aureus* isolates, from 18 percent to 3 percent, correlated with the hospital's policy on the use of Erythromycin. In a burns treatment unit in which topical Gentamicin had been in use since 1964, only 9 percent of *Pseudomonas aeruginosa* were susceptible in 1969. In late 1969, the use of topical Gentamicin was discontinued, and by the following year

only 5 percent of *Pseudomonas aeruginosa* isolates were resistant to Gentamicin.[9] On the other hand, a comparison of antimicrobial use and resistance between two hospitals in Sweden and Lithuania concluded that a high antimicrobial pressure in a single hospital *per se* does not necessarily promote resistance and other factors that must be considered and are subject to further study include the total antimicrobial pressure in the community, adherence to guidelines for doses and duration of antimicrobial treatment and spread of resistant clones and other issues related to good infection practices.[81]

1.2.7 Cost of antimicrobial resistance and health care associated infection (HAI)

The annual cost associated with antimicrobial resistance in the United States was estimated to be between USD 100 million to 30 billion in 1989 and USD 157 million to 47 billion in 1999.[91] The wide range of costs is likely resulted from implementation of direct or indirect costs and uncertainties with cost analysis in general. In United states, HAI per 1000 patient days increased by 36% between 1975 and 1995. Furthermore, it has been estimated that there are approximately 88,000 deaths attributed to HAI annually, ranking it as the fifth leading cause of death in acute care hospitals.[92] These trends suggest that many challenges still exist in the prevention and control of HAI in the health care setting. The total annual hospital-related financial burden of HAI in the United States was estimated to exceed USD 4.5 billion in 1992, USD 6.5 billion in 2004 and Euro 9 billion in Europe.[93, 94]

A multicentre study in the United States showed that MRSA infections caused a 10% higher mortality rate and a USD 3,500 per patient cost increase compared with Methicillin Susceptible *Staphylococcus aureus* (MSSA). The same data for Vancomycin Resistant Enterococci (VRE) infections indicated a 39% higher mortality rate and USD 100,000 per patient increase compared with Vancomycin Susceptible Enterococci (VSE) infections.[91]

In a systematic review of economic analyses of health care-associated infections on publications from 2001-2004, attributable costs were USD 25,546 for surgical site infections (8 studies), USD 36,441 for blood stream infections (9 studies), USD 9,969 for ventilator-associated pneumonia (2 studies) and USD 1,006 for urinary tract infections. [93]

In the UK, the cost of containing an MRSA outbreak in a single hospital was estimated at over GBP 400,000.[58] Hospital-acquired infections were estimated to cost the NHS in England GBP 986.36 million annually.[95] In 2001, hospitals across Scotland needed 243,000 more bed-days to clear their waiting lists completely. At the same time it was estimated that over twice as many bed days (517,000) were occupied because of HAI and that eliminating HAI would free up 1,420 beds in acute services. The annual cost of the additional 9.2 days length of hospitalisation due to HAI was estimated to be £183 million per annum in Scotland in 2005/2006.[96, 97]

On the other hand, there are concerns about the reliability of methods in estimation of economic burden of HAI. Differences in methods used to estimate costs, which has been a chronic problem found in economic evaluations, contributes to the wide range of costs reported. Furthermore, in many publications the costs include estimates of hospital costs only, not costs to the broader health care sector or to society. High estimates of costs, designed to push decision makers into action, may do more harm than good in the struggle to attract funding for infection control. Expectations among policy makers might be raised, and then they are disappointed when the reduction in the number of HAIs does not yield the anticipated cost saving.[93, 98]

1.2.8 National and International recommendations

The problem of antimicrobial resistance crosses boundaries and requires concerted action against a global problem. Thus the "Copenhagen Recommendations" were released after the European Union conference on The Microbial Threat in Copenhagen, 1998.[44] This conference identified the lack of information about, and the lack of surveillance of, resistance and the importance of bridging this gap in knowledge and monitoring. Although the information generated about antimicrobial usage and key infection control practices provide the basis for development of codes of good practice, the availability of antimicrobial consumption data to the public health authorities and scientists is very limited. Accordingly the Copenhagen Recommendations focused on data collection, including;

- Data on antimicrobial resistance over time or prevalence.
- Consumption data over time or prevalence.
- Correlation between consumption and resistance.

Consumption data should be used to develop therapeutic guidelines appropriate to local need, and to form the platform on which educational and other interventions can be built. These data are important triggers for action and investigation and consequently, more coherent and well-funded research initiatives are needed.[44] Recommendations were re-emphasised by the 2001 report, "Acting on the Council of the European Union Recommendations on the Prudent Use of Antimicrobial Agents in Human Medicine".[99]

The Pan-European recommendations resulted in funding for research projects. Antimicrobial Resistance: Prevention And Control (ARPAC) was a research project funded by the European Commission.[100] This project was developed by four European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study groups and

aimed to identify antimicrobial policies, prescription patterns and infection control policies associated with lower rates of antimicrobial resistant pathogens at the individual hospital level. ARPAC had some shared aims with two other EC funded projects: the European Antimicrobial Resistance Surveillance System (EARSS) and European Surveillance of Antimicrobial Consumption (ESAC). The three project leaders have therefore agreed to work in close collaboration (sharing data and using the same methodology).[101]

The European Union (EU) Council Recommendation on patient safety including the prevention and control of healthcare-associated infections were adopted by EU Health Ministers in June 2009 and listed a series of actions in this area.[102] Ten years after Copenhagen conference and call for action it was claimed that Europe was showing the way on turning the tide of antimicrobial resistance.[103] Nonetheless, in November 2009, EU and US, agreed to establish a transatlantic task force on urgent antimicrobial resistance issues focused on appropriate use of antimicrobials and prevention of health-care. This implies that the current situation on antimicrobial resistance, among all medical and health related topics, is a global challenge besides the financial crisis, climate change and war in Middle East.[104]

In the UK, in 1998, the Standing Medical Advisory Committee published “The Path of Least Resistance” to identify the main problems faced in reducing antimicrobial prescribing. The report pointed out that "…regimens of antimicrobial vary hugely from hospital to hospital often with no underlying rationale[105]. Following the House of Lords Select Committee on Science and Technology report in 1998, there was a national drive to reduce antimicrobial prescribing. Nonetheless, the House of Lords reported that rather to their dismay, data on antimicrobial use in hospitals which had been unsatisfactory in 1998, were no better in 2001.[24, 106]

In 2002, the Scottish Executive Antimicrobial Resistance Steering Group was established to gain commitment to a co-ordinated, focused approach at the local, national and international levels for prudent antimicrobial use in humans and set the surveillance of antimicrobial use and resistance as one of the key elements.[107]

1.2.9 Conclusion: the importance of evaluation of antibiotic use in hospitals

Antimicrobials are unique amongst drugs in that they target "infectious" or "transferable" diseases. Resistant bacteria do not know the boundaries, either between countries or within a society between hospital and primary care. Inappropriate prescribing of antimicrobials in hospitals therefore has consequences for the whole community that the hospital serves and problems may spread both nationally and internationally. A few years ago it was thought that reversal of resistance could happen after a relatively short time of reducing antimicrobial use pressure but it is now clear that this is not necessarily true. However, in the confined environment of hospitals prudent use of antimicrobials has the greatest potential for reversing collateral damage. Hospitals are a critical component of the antimicrobial resistance problem worldwide. The combination of vulnerable patients, intensive and prolonged antimicrobial use, and cross-infection have resulted in nosocomial infections with highly resistant bacterial pathogens. Resistant hospital-acquired infections are expensive to control and difficult to eradicate. Given the recent worldwide escalation in resistance, and the overwhelming clinical and economic effects of inappropriate usage of antimicrobials, the pragmatic and essential approach to the control of resistance is the control of antimicrobial use. It follows that reliable measurement of antibiotic use in hospital with standardised methods will be essential to building the evidence base and highlighting inconsistencies at national and international levels (Figure 1.1, Table 1.1). The next section identifies important gaps in the evidence about hospital antibiotic use.

1.3 Methods & Gaps in Hospital Antibiotic Use Measurement

1.3.1 Introduction

In this section methods applied to hospital antibiotic use measurement are reviewed. The aim is to identify gaps in the evidence and the need for additional valid, comparable and feasible methods. Firstly, key elements of standard measure are described. Secondly, different methods in the study field are reviewed to identify those can be implemented and improved for this thesis.

Different methods and measurements have been applied to Drug Utilisation Research (DUR) of antimicrobials in hospitals depending on the aims and availability of data. DUR studies have been carried out to identify the problems within institutions,[108-115] to allow benchmarking between institutions,[81, 116-119] to allow follow up and compliance with the guidelines,[120-124] to assess appropriateness,[123, 125-127] to estimate the costs of antibiotic therapy,[25, 111, 127, 128] to evaluate changes over time,[28, 114, 129-132] and to evaluate organisational changes.[122, 133] Nonetheless, despite this extensive experience some gaps and shortcomings are not usually addressed.

1.3.2 Quality criteria of outcome measure

Whatever the aims of DUR studies are, and regardless of the size and number of hospitals included in the studies, the choice of outcome measure is a central issue.

There are well established criteria for assessing the quality of an outcome measure that could be considered before choosing the measures and methods.[134-136]

1 Discrimination: Reliability and Responsiveness - It indicates the related concepts of reliability (the degree to which a result obtained by a measure can be replicated) and sensitivity to change, which is also known as responsiveness. All else being equal,

a measure that has poor reliability (because most variation in it is due to random error) will also be less responsive. The study design determines whether the objective is to determine the stability of a measure (reliability) or its ability to respond to external change (responsiveness). Reliability should be reported using both relative and absolute statistics because they provide different information and are subject to different biases depending on the study design and subjects. Responsiveness can also be reported using several methods.[134-136] Discrimination is the degree to which a measure is good at differentiating high from low. It has been argued in literature if the discrimination and reliability are the same or difference.[137]

2 Validity - Is it valid for the purpose? In simple terms, validity is the extent to which an instrument measures what is intended. There are three types of validity to consider: content, criterion and construct. Content validity or comprehensiveness is the extent to which the items in the scale adequately represent the domain being measured (e.g. how does the total cost of antibiotics represent all manifestations of the antibiotic use). Content validity is evaluated qualitatively through a combination of consensus expert opinion, interviews with patients and literature review. Criterion validity addresses the question of whether a measure agrees with (concurrent criterion validity) or predicts (predictive criterion validity) a "gold-standard" measure of the same and different attributes. Construct validity refers to how well the instrument measures what is intended. It is evaluated by analysing the relationship between the measure and other measures of the same and different attributes. Accuracy of the data, data processing, satisfactory statistical method, and adequate sample size are key components of validity. [134-136]

3 Feasibility - Can the measure be applied easily, given the constraints of time, money, interpretability, acceptability to all users and ethics?[134-136]

1.3.3 Patient Specific Data and Measures

The first audits on hospital antibiotic use were obtained from patient records within institutions or specialties. They were mainly focused on the evaluation of either a single or a group of antimicrobials prescribed for a given indication and sought to identify or evaluate the appropriateness of treatment at baseline and after an intervention, and to evaluate costs.[25, 109, 115, 132, 138-143] These audits were successful in identifying the problem and contributed to quality indicators for hospital antimicrobial use. In some of these studies, computerised patient records were used, making the surveys more precise.[144-147] Most of these studies reported that the interventions were cost saving. [25, 132, 138, 143, 144] However, these studies do not provide enough detail about the cost of design and implementation of the intervention to allow other hospitals to estimate the cost of repeating the same intervention.[148]

A limitation of the studies was that they extracted data from patient records. Several studies have shown that information extraction was not complete [149-151]. Extracting data from patient records is subject to personal interpretations, even within one institution. This issue needs more investigation when the outcome is appropriateness of antimicrobial treatment. The level of agreement, even with clear criteria, also varies according to personal judgments.[152] These studies are limited in reproducibility because they are mainly focused on addressing a specific problem of concern at a given time. Additionally, some studies were not repeated over time and cannot be applied to other institutions within the same country or at international level. The same measures may not be available in other hospitals or in the same hospital at different times.

When used for cost assessments, these studies have limited reproducibility if not adjusted for price changes over time and different pricing systems in other institutions within the same country and in other countries. Also focusing on cost may exaggerate

the impact of new and expensive drugs and may mask important changes in patient exposure to cheaper and older drugs. Introducing guidelines targeted at specific antimicrobials may shift the use to other agents and, therefore, monitoring of the broader group of antimicrobials is essential while assessing the outcomes.

1.3.4 Point Prevalence Surveys

Point Prevalence Survey (PPS), a single measurement at one point in time was introduced in the 1980s and since then, has become a widely used method to assess hospital antimicrobial use and hospital infection at the patient level [150, 153]. PPS is a feasible, inexpensive method that provides rapid results. This kind of survey is usually carried out on a single day. Patient records are used to identify prescribed antimicrobials, dosages, indications, infection sites and diagnoses. It is an easy method to allow understanding of the problem and, over time, highlights a number of areas for improvement and benchmarking within or between hospitals. On the other hand, because this method allows rapid analysis, it is becoming a valuable tool for timely feedback to clinical groups and physicians. Rapid feedback of PPS usually brings more organisational support for further surveys.

In a few European countries, PPS is carried out on a regular basis once or twice a year. Computer based data collection and analysis can make PPS even easier and less time consuming. A few studies proved that handheld computers are cost effective tools in survey studies. However, in the early stages they may encounter errors without any possibility of correcting them.[154-156]

As mentioned above, these studies can have their limitations – such as data extraction and personal interpretations made by auditors from the patient records and data collection forms. The survey team may include infectious disease specialists,

pharmacists, microbiologists, infection control nurses and epidemiologists. It is possible that each of these disciplines has different attitudes towards the importance and interpretation of specific data items. For example pharmacists are more likely to look for information related to the appropriateness of the prescribed antimicrobial whereas infectious diseases specialists may be more focused on the diagnosis of infection. Finally, in published studies it is usually unclear as to the amount of resources allocated to the process of agreeing what information will be asked for during the data collection phase.[148]

PPS assessing antimicrobial treatment on a single day can reasonably represent the most common indications and the most commonly used antibacterials. However, examination at single point in time may underestimate or overestimate the frequency of use of less common drugs.[157] In a PPS in Tayside and Glasgow Health Boards, there were only a few prescriptions for antibiotics classed as Alert Antibiotics, antimicrobials included in most prescribing stewardship programmes.[158] Although all PPS measure the prevalence of antibiotic therapy, studies often use different measures making comparison across studies and institutions difficult (Table 1.2). PubMed was searched for Point Prevalence Surveys in European countries either in single hospitals or multicentre and national surveys. Eighteen studies were identified[116, 117, 153, 158-172] and the content of each study was compared with the annual point prevalence survey in Swedish hospitals co-ordinated by STRAMA (The Swedish Strategic Programme for Rational Use of Antimicrobial Agents and Surveillance of Resistance).[161] None of the other studies contained all of the information collected by the STRAMA surveys (Erntell 2003 and 2004 in Table 1.2). Eight studies excluded surgical prophylaxis, four studies only included adults and four studies only included children (Table 1.2). These differences make it very difficult to compare results between studies and countries.

Table 1.2: Published Point Prevalence Surveys from European countries

Study	Year	Country	Hospitals	Surveys	Population	Patients	Surgical	Prevalence	Site of	Prescribed	Route of
Cook [153]	1983	UK	1	1	All	921	Included	21%	N	N	N
Astagneau [159]	1999	France	23	1	Adults	6839	Excluded	Not given	Y	N	N
Berild [160]	2002	Norway	1	12	Adults	6588	Included	16.6%	Y	Y	N
Erntell [161]	2003	Sweden	19	1	All	4178	Included	30.9%	Y	Y	Y
Erntell [161]	2004	Sweden	18	1	All	3622	Included	31.9%	Y	Y	Y
Bugnon-Reber [162]	2004	Switzerland	8	1	All	695	Included	25%	N	N	N
Ufer [163]	2005	Croatia, Germany	2	1	Children	600	Included	17.4%	y	N	N
Usluer [164]	2005	Turkey	18	1	All	9471	Included	30.6%	N	N	N
Pujate [165]	2005	Latvia	7	1	All	3150	Excluded	27%	Y	N	N
Vlahovic-Palcevsky [116]	2006	Croatia, Estonia, Latvia, Lithuania, Sweden	5	1	All	4138	Included	24.8%	Y	N	N
Hajdu [166]	2007	Russia	1	1	Children	472	Included	39.0%	N	N	N
Seaton [158]	2007	UK	10	1	All	3826	Excluded	28.3%	Y	N	Y
Dumpis [117]	2007	Latvia, Lithuania, Sweden	3	1	All	1611	Included	26.4%	N	N	Y
Willemsen [167]	2007	Netherlands	1	6	All	4105	Excluded	22.9%	N	N	N
Ang [168]	2008	UK	1	1	Children	359	Included	49.3%	Y	N	N
Degli Atti [169]	2008	Italy	1	1	Children	412	Excluded	43.9%	N	N	N
Diminia [170]	2009	Latvia	7-12	5	All	18,226	Excluded	26.9%	N	N	Y
de With [171]	2009	Germany	1	1	Adults	941	Excluded	28%	N	Y	Y
O'Neill [172]	2009	N. Ireland	1	1	All	529	Excluded	36.8%	N	N	N

1.3.5 Aggregated data using pharmacy dispensing database

While patient specific data for inpatients are still difficult to obtain on a continuous basis, pharmacy dispensing data are available monthly or quarterly in most hospitals. These data allow comparison over time and place and longitudinal surveillance of antimicrobial use. This source has been widely used since the 1970s with different measures and different methods. As a result of computerised data in hospitals in recent decades, this information has become easier to obtain.

Quantitative measures in terms of grams can be meaningful for a single drug but cannot be used for aggregated use or to compare the use of different antimicrobials. The number of dispensed packages has even lower value, even for measuring the use of a single drug. The cost of antimicrobial use is often used as a measure of antibiotic use. This measure usually highlights expensive antimicrobials. Furthermore, as mentioned above, costs should be adjusted for changes in prices over time, especially in longitudinal studies. It is not a valid measure for international comparisons and even for local benchmarking in some countries. Using dispensing information without converting the data to doses cannot provide meaningful data. Pharmacy stock data, even if converted to doses, have some limitations. Dispensing data may overestimate exposure as a result of drug wastage or expiration in ward stock, not accounting for returned drugs or inclusion of outpatient drug use associated with outpatient clinics or prescribing on discharge. In some countries not all antimicrobials are always available from the hospital pharmacy and they may be supplied out of hospital. In these countries pharmacy dispensing data underestimates the total use. In some of the published DUR studies, differences in hospital characteristics are not mentioned or regarded. Pharmacy information at patient level is becoming available in more hospitals but is still only available in a minority of hospitals in any European country. When these data are not

available, pharmacy dispensing data is the most commonly available data in hospitals but should be interpreted with caution.

The WHO Collaborating Centre for Drug Statistics Methodology was established in Oslo in 1982 to improve and manage the Anatomical Therapeutic Chemical classification (ATC) ATC/DDD system that had been recommended by the WHO Regional Office for Europe for international drug utilisation studies in 1981. In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.[173] The basic definition of the Defined Daily Dose (DDD) unit is: the assumed average maintenance dose per day for a drug used for its main indication in adults. The WHO Centre emphasises that "the defined daily dose is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. Doses for individual patients and patient groups will often differ from the DDD".[1, 174] In further publications the WHO Centre reviewed the studies using ATC/DDD. They found that in many studies, changes in ATC/DDD are not considered and the ATC/DDD version has not been referenced. They also emphasised that the DDD is a technical unit of measurement.[175]

The DDD is implemented to produce a quality indicator of antimicrobial use in hospitals or primary care is DU90%. DU90% reflects bulk indices of antimicrobial utilisation.[4] It is applied to hospital antimicrobial consumption for local, national and international comparisons and monitoring of antibiotic use and resistance, identifies impact of change programmes and adherence to guidelines. DU90% can be used with routinely available data in any hospital derived from pharmacy stock data or prescribing at patient level.[5, 118, 122, 176-180]

For normalised information about hospital drug use, the WHO Centre recommended occupied bed-days as a denominator since this information is available in many hospitals from hospital administrative data.[174] Accordingly, the recommended measure is DDD/100 bed-days. Since then this measure has been widely used in DURs of antimicrobials in hospitals, and recommended for use at national level in most countries and at international level. The reasons are feasibility, reproducibility, discrimination, easily achieved organisational support, continuity and regularity, and, to some extent, relevance to usual practice. DDD/100 bed-days are used for benchmarking, evaluation of changes over time and effectiveness of interventions.[175] Nevertheless, the WHO Centre has observed discrepancies between studies due to the use of different ATC/DDD versions, comparing studies with different DDDs for one substance, and miscalculations.[181, 182]

Other problems associated with the DDD measure are a result of misunderstandings in comparative studies. In some benchmarking studies on the total use of antimicrobials, a decrease in use was interpreted as better practice without taking account of the variety of antimicrobials contributing to total use. The proportion of ICU beds, presence of haematology specialties, paediatrics, and renal units can affect the level of use. In some studies these basic hospital characteristics are not considered in the interpretation of the results.

The Antibiotic Resistance, Prevention and Control (ARPAC) 2002-2004 was a European project that used antimicrobial use and resistance data from 170 hospitals in 31 countries.[100] The project introduced the Anti-Bacterial Consumption (ABC) calculator for systemic antibacterials, class J01 in ATC classification. ABC is an Excel sheet with a designed formula for calculating DDD/100 bed-days. The user should enter the total volume of each antibacterial used in grams together with the number of bed-

days. However, the ARPAC project revealed significant errors in the calculation of both numerator and denominator. Assigning the correct ATC, dealing with trade names, and different coding systems in each hospital pharmacy are problems that can lead to miscalculations. In one of the publications from this project[183], the authors provide examples of miscalculations arising from incorrect entry of raw data. These clearly illustrate two fundamental problems. First the resulting errors can be very large because of multiplication factors. Second, even very extreme results were not identified as being implausible by the staff responsible for data entry. Comparison across countries and hospitals therefore requires both careful training of local data collectors, and a central checking process.

1.3.6 Longitudinal surveillance measures: numerators and denominators

The literature is confusing because of the use of apparently similar but actually different numerators and denominators. For example, in 1998 a multi-centre study in the United States reported antibiotic use in Intensive Care Units as DDD. However, the measure was actually the average Prescribed Daily Dose rather than the WHO DDD. For example the "DDD" for parenteral ampicillin in this study was 4g[184] whereas the actual WHO DDD is 2g.[185] In a recent study in 130 US hospitals, Days of Therapy (DOT)/1000 patient-days was introduced and compared with DDD/1000 patient days. The authors recommended using DOT/1000 patient-days instead of DDD/100 patients-days.[186] However, longitudinal measurement of days of therapy requires electronic access to patient specific prescribing data and this is not available in most European hospitals. In two studies conducted in UK hospitals, authors introduced DDD per finished consultant episode (FCE) for antimicrobial use in hospital.[187, 188] An FCE is a continuous period of time an admitted patient receive care under one consultant, or one consultation team, within one healthcare provider. DDD/FCE was used as a measure to

evaluate an intervention indicator in one of the studies [187] and compared with DDD/100 bed-days [188] in the second one. The FCE data are available in England and Scotland and each Trust processes their data slightly differently therefore this denominator cannot be applied to international studies. Additionally, because one patient can be under care by two or more consultation team at the same time data FCE may bias results.

Most longitudinal studies of hospital antibiotic use have used DDD/bed-days or DDD/patient-days and have applied the WHO ATC/DDD classification. However, recent studies have questioned the validity of only using bed days or patient days to adjust for clinical activity. In 2005, two longitudinal surveys in Dutch hospitals were performed to find and examine an additional measure to quantify antibiotic use in hospitals. The authors concluded that DDD/100 bed-days overestimates antibiotic use compared with DDD/100 admissions because of a systematic reduction in mean length of hospital stay over the study period. These studies made the point that while DUR researchers are looking for a more clinically meaningful numerator, a different denominator can change the trends over time and affect the whole interpretation of longitudinal and benchmarking surveys. They authors suggested using both denominators to evaluate change in antibiotic use.[189, 190] A limitation in both of the studies was the statistical analysis of trends, which used simple linear regression of aggregated annual data.

An additional study in one German hospital reported similar results over 12-year longitudinal data, with systematic reduction in mean length of stay and widening gap between DDD/100 bed days compared with DDD/100 admissions. However, statistical analysis was limited to comparison of the average use in the first three years *versus* the last three years.[191] Comparison of two denominators of clinical activity was also used

in two published study form Switzerland.[192, 193] However, in these studies "admissions" included transfers between clinical departments in the same hospital and was therefore likely to introduce similar biases to the Finished Consultant Episode used in England. Collectively these studies recommend use of both admissions and bed days as denominators for surveillance of antibiotic use but they do not provide a robust statistical method for analysis of trends over time either within or between hospitals.[189-193]

1.3.7 Conclusions: gaps in the evidence and methods used in this thesis to close the evidence gaps

No single measure can currently capture all of the aspects of hospital antibiotic use. However, a combination of detailed, point prevalence data from individual patients with longitudinal analysis of total consumption could provide meaningful data for comparison between hospitals and for analysis of the relationship between use and outcome. This approach would also inform the development of electronic prescribing records for individual patients because it would define the minimum dataset that is required to support the initial prescription of an antibiotic, capture the outcome of prescribing and determine roles and responsibilities at each point in the care pathway. However, the evidence reviewed identified significant problems with standardisation of data collection, statistical analysis and interpretation that need to be addressed for both longitudinal surveillance of total antibiotic use and point prevalence of individual patient use.

Guides to chapter 2- 8

In Chapter 2 I review the literature on methods for statistical analysis of time series and interrupted time series and identify those that could be applied to longitudinal surveillance of antibiotic use in hospitals.

Chapter 4 is a brief overview of the ESAC (European Surveillance of Antibiotic Consumption) and the opportunities provided for collaboration on longitudinal and point prevalence surveys.

The justification for chapters 3 and 5 to 8 of the thesis is summarised below in the form of the research questions posed and the contributions made to close the gaps in the evidence identified in Chapter 1.

Chapter 3

Interrupted time series analysis of an intervention to reduce unnecessary use of Alert Antibiotic in NHS Tayside

Research Question 3.1

> What is the impact of an Alert Antibiotic policy on the use of antibiotics reserved for second line treatment of resistant organisms?

Research Question 3.2

> What is the cost of designing and implementing the policy and to what extent are these costs offset by savings in drug costs?

Contribution 3.1

A method for electronic conversion of drug supply data to the ATC/DDD classification and for longitudinal analysis that can be applied to data from other hospitals

Contribution 3.2

A template for documentation of the cost of design and implementation of an intervention

Contribution 3.3

A method for standardisation of antibiotic cost data over a four year period

Chapter 5

ESAC longitudinal survey 1: analysis of total antibiotic use

Research Question 5.1

What is the change in hospital antibiotic use over the study period?

Research Question.2

What effect do different denominators (bed days or admissions) have on longitudinal analysis of hospital antibiotic use?

Contribution 5.1.

A method for standardising and processing data from multiple hospitals and different countries.

Contribution 5.2.

A plan for multivariable analysis of time series and comparison of the impact of different measures of clinical activity on hospital antibiotic use.

Chapter 6

ESAC longitudinal survey 2: comparison of total, parenteral and broad-spectrum antibacterial usage

Research Question 6.1

Are the same time trends present in use of total antibiotics, parenteral antibiotics and antibiotics with high risk of collateral damage?

Contribution 6.1

Application of the method for multivariable analysis to comparison between trends for different antibiotics.

Chapter 7

ESAC point prevalence survey of antibacterial use

Research Question 7.1

Can the STRAMA methods be applied in other European countries?

Research Question 7.2

What is the PDD (Prescribed Daily Dose, the actual daily doses prescribed in each hospital) and how does this compare with the WHO DDD for antibiotics used in European hospital?

Contribution 7.1

Test of the feasibility of using a web based reporting system for collection of data from multiple countries.

Contribution 7.3

A method for comparison of DDD with PDD data from multiple hospitals.

Contribution 7.2

Application of a statistical method for analysis of variance to ranking of hospitals for prevalence of antibiotic use.

Contribution 7.3

Identification of potential quality indicators for hospital antibiotic use.

Chapter 8

Research Question 8.1

To what extent does variation in hospital characteristics explain variation in antibiotic use?

Contribution 8.1

Test of the feasibility of collection of data about hospital characteristics

Contribution 8.2

A plan for statistical, multivariable analysis of the association between hospital characteristics and antibiotic use as measured by point prevalence or total consumption.

Chapter 9

Review of potentials of this thesis in implementing new methods to improve indicators of hospital antimicrobial use.

Review the impacts of the studies on providing evidence of practice profile and to change programmes.

State the overall weakness and limitations of thesis and suggestions for further research.

Recommended further studies.

CHAPTER TWO: Time Series and Interrupted Time Series Analyses

2.1 Introduction

A time series is a sequence of measurements that follow a non-random order. Time series analysis is an application which was mainly conceptualised in economic studies, but is increasingly implemented in public health and bioscience. A search of PubMed for the term "time series analysis" in the titles or abstracts of English publications identifies 234 papers before 1990 and 1,501 from 1990 to 2010.

Analysis of time series may have different goals including: to identify the pattern in a sequence of observations over time and the context of underlying process; to examine the impact of interventions; and to forecast the future pattern of events or to compare series with different kind of events.

The application of time series analysis methods is multifaceted and varied in nature rather than a homogeneous set of statistical techniques. In experimental designs, interrupted time series analysis (ITSA) refers to analysis of time series to estimate the outcomes of a change in policy or an intervention. The application of ITSA in medical sciences is increasing. A search of PubMed retrieves 14 papers before 1990, and 116 papers from 1990 to 2010.

This chapter provides an overview of time series concepts, analysis methods, and statistical approaches. Later in the chapter, interrupted time series analysis is described. These methods are used in chapters 3, 5, and 6 of this thesis.

2.2 Time Series Analysis

A time series is a sequence of data points, measured typically at successive times, spaced at uniform intervals. Sometimes the observations are from a single case but more often they are aggregated from many cases. One of the concepts that make possible the use of probability in time series is the assumption of stationarity. The stationarity implies that the individual observations all have the same univariate distribution, in particular, same mean and variance which do not change over time. Under this assumption, we can use the replication over time in a time series to make inferences about the common mean, variance and other statistics. When the series are not stationary they contain *unit root*.[194, 195] Later in this chapter the methods for making a non-stationary series to stationary are described.

Time series analysis comprises methods that attempt to understand such time series. Box and Jenkins[196] introduced an approach to statistical analysis for time series that accounts for autocorrelated series where successive data points are correlated, with three steps 1) Identification2) Estimation and 3) Diagnosis.

1) Identification

In first step, identification, Autocorrelation Functions (ACFs) and Partial Autocorrelation Functions (PACs) are examined for presence of autocorrelation, trend and seasonality in the series. ACF and PACF are explained in section 2.3. In the identification step, the ACF and PACF are examined whether or not the series are stationary. When series are found to be stationary, have the same mean and variance which do not change over time, then the plots are examined again to distinguish the Autoregressive (AR) and Moving Average (MA) in the series and if this is the case then

to identify the order of AR and MA, or the degree to which successive points are correlated. AR and MA are more fully explained later.

2) Estimation

In the second step, estimation, the analyst uses a series of statistical modelling to estimate parameters of the particular model. The order of autoregressive, moving average and their effects are tested against the null hypothesis of zero.

3) Diagnosis

In the third step, diagnosis, residuals are examined to determine if there are still patterns in the data that are not accounted for. This includes examining of the residual from the model using ACF and PACF plots. Residual scores are the difference between the predicted values by the model and the actual values. Provided that all autocorrelations are captured by the model then the residuals plot should be consistent with a pure random process. In time series analysis, power depends on the accuracy of the model. [196] In addition to other outputs of a fitted model there are two criteria to measure goodness-of –fit. The Akaike Information Criterion (AIC) is a measure of goodness of fit for an estimated model. It is often used in model selection. Smaller values of the AIC are preferred. For example, you can choose the length of a lag distribution by choosing the specification with the lowest value of the AIC. The Schwarz Bayesian Criterion (SBC) is an alternative to the AIC that imposes a larger penalty for additional coefficients. The ratio of AIC to SBC should be close to one.[195, 197] An example of time series fitted model and output parameters is will be described in Chapter 3.

When the best equation is identified through estimation and diagnosis steps and statistical tests that are described later in this chapter either on the model or on residuals, the formula can be used to predict or forecast and it is application of many time series

analyses in an economic arena. However, in healthcare analyses, the goal is often to assess the impact of interventions, both naturally occurring and quasi-experimental. [196, 198]

2.3 Autocorrelation

Autocorrelation is likely to be present in time series. When data are ordered in chronological order, the error in one period may be associated with the data in another time period or the next time point. In time series, autocorrelation means that errors or residuals of the fitted model are correlated with each other in particular lags. Autocorrelation may be positive or negative. The presence of autocorrelation violates the assumption in Ordinary Least Squares (OLS) of independence where the correlation between errors over time is zero. One of the important tools for identifying the presence of autocorrelation is the correlogram. Usually two types of correlograms are examined to identify the presence of autocorrelation: 1) the Autocorrelation Function (ACF) and 2) the Partial Autocorrelation Function (PACF). ACF is a simple and unconditional correlation between a time series data point and its lags.[197]

Visual examination of ACF and PACF plots are used to describe and identify the series and prediction of the model. If an autocorrelation at some lag is significantly different from zero, the correlation is included in the model and if the condition applies to partial autocorrelation it will be included too. [198]

One factor that can cause autocorrelation is omitted variables. If the omitted variable is correlated with previous observations, then this will lead to unavoidable correlation between consecutive error terms. Autocorrelation can also occur due to misspecification of the model. Suppose that the Y_t is connected to X_{2t} with a quadratic relationship but we wrongly specify a linear relationship, then the error term will

increase or decrease with x_{2t}, indicating autocorrelation. A third factor is systematic error in measurement. In this case the series will contain a cumulated measurement errors causing autocorrelation. Presence of autocorrelation can be a combination of those factors.[195]

2.3.1 Statistical tests for autocorrelation

In addition to examining the ACF and PACF plots there are also a number of formal statistical tests to identify autocorrelation in the series.

Box and Jenkins [196] presented Q statistics in their time series modelling. For a given lag length N, the null hypothesis is that no lags up to and Including N contain an AR and MA parameter which is significantly different from zero. A limitation of Q statistics is that with high lag lengths N, or degrees of freedom, the power of this test to reject the null hypothesis is quite low. In fact it is possible that the ACF plot shows a marked spike but the while the Q statistics is insignificant.[196] Therefore, it is not a good idea to rely on Q test.

Another test for presence of serial (first order) autocorrelation is the Durbin-Watson (DW) test (1950, 1951 and 1971). Under the null hypothesis of no autocorrelation (P = 0), DW is equal to or around 2. A test statistic below 2 suggests positive autocorrelation ($P > 0$), while a test statistic above 2 suggests negative autocorrelation. There are two other critical values which allow a degree of uncertainty in testing the hypothesis; a smaller value DW_L and a larger value DW_H. Tables containing DW_L and DW_H for various sample sizes and number of repressors are contained in many econometrics text books.

To test for positive autocorrelation, we do not reject the null of no autocorrelation if $DW > DW_H$, and we reject the null in favour of the alternative hypothesis that $p> 0$ if

$DW < DW_L$. If DW lies between DW_L and DW_H, the test is inconclusive; in that case, alternative tests for autocorrelation should be considered.

Although less common than positive autocorrelation, negative autocorrelation can also be detected using the Durbin-Watson statistic. If $DW < (4 - DW_H)$, the null hypothesis is not rejected. If $DW > (4 - DW_L)$, the null is rejected in favour of the alternative that $p< 0$. If $(DW_H -4) < DW < (DW_L – 4)$, the test is inconclusive. [199]

The DW test has several drawbacks that make its use inappropriate in various cases. [195] For instance, it may give inconclusive results, it is not possible to be used with a lagged dependent variable as an explanatory variable, and it cannot be used where there are higher than first order autocorrelation.

This test is valid when:

- The regression model includes a constant
- Serial autocorrelation is assumed to be first order only , and
- The equation does not include a lagged dependent variable as an explanatory variable.[195]

The Lagrange multiplier test of Breusch (1978) and Godfrey (1978) and Durbin's (1970) alternative test are two tests for serial correlation that relax the requirement that the regressors be strictly exogenous (so that the model can contain lagged dependent variables as regressors), test for the possibility that the residuals follow an AR(*p*) or MA(*p*) process, so there is no indeterminant region. Both tests are based on fitting equation by OLS, collecting the residuals, then fitting the regression [199] .

2.3.2 Types of autocorrelation

Two distinct types of autocorrelation are identified: 1) autoregressive process and 2) moving average process.

In an autoregressive process, the ACF plot dampens out relatively quickly while the PACF plot has large spikes at lag points with near zero spikes at subsequent lags. The order of the autoregressive process, *p*, is defined by number of large spikes. For example an AR process of order 2 has two large spikes in PACF. Nonetheless, in practice ACF and PACF plots are not usually as clear as typical plots.

In contrast a Moving Average (MA) process is identified by a PACF plot which dampens quickly or relatively quickly and an ACF plot with large spikes at lag order q.

It is also important to consider the extent of autocorrelation provided by AR and MA models. In both processes the limits of autocorrelation must meet bounds within -1 and +1 limits. For AR process this limit is called bounds of stationary while for MA process it is called bounds of invertibility. [199] Bounds of invertibility and stationarity are described later in the chapter.

Tables 2.1 summarises the different shapes in ACF and PACF plots and the most possible explanation for them for a times series consisting of 10 time points[198] . The three values in the parenthesis are the orders of the nonseasonal autoregressive (AR) or *P*, differencing or *d*, and moving average (MA) or *q* operators, respectively. These are three components of ARIMA(Autoregressive Integrated Moving Average) and ARMA (Autoregressive Moving Average) methods are later described in this chapter. There are two common ACF patterns. There may be constant spikes Table 2.1 (a), or there may be a “damped sine wave” Table 2.1 (b), in which spikes oscillate first on one side and then on the other side of zero. [198]

Table 2.1: ACF and PACF for Common ARIMA Models. Adapted from Tabachnick et al. 2000.[198]

Model	Lag	ACF			PACF		
		–	0	+	–	0	+
ARIMA (1, 0, 0)	1		|_____			|_____	
	2		|_____			|	
	3		|____			|	
	4		|___			|	
	5		|_			|	
	6		|			|	
	7		|			|	
	8		|			|	
	9		|			|	
	10		|			|	
ARIMA (0, 0, 1)	1		|_____			|_____	
	2		|			|_____	
	3		|			|_____	
	4		|			|___	
	5		|			|_	
	6		|			|	
	7		|			|	
	8		|			|	
	9		|			|	
	10		|			|	
ARIMA (2, 0, 0)	1		|_____			|_____	
	2		|_____			|_____	
	3		|_____			|	
	4		|____			|	
	5		|_			|	
	6		|			|	
	7		|			|	
	8		|			|	
	9		|			|	
	10		|			|	
ARIMA (0, 0, 2)	1		|_____			|_____	
	2		|_____			|_____	
	3		|_____			|_____	
	4		|____			|____	
	5		|_			|___	
	6		|			|_	
	7		|			|	
	8		|			|	
	9		|			|	
	10		|			|	

		ACF			PACF		
Model	**Lag**	–	0	+	–	0	+
ARIMA (p, 0, q)	1		|_____			|_____	
	2		|_____			|_____	
	3		|_____			|_____	
	4		|_____			|_____	
	5		|_____			|_____	
	6		|_____			|_____	
	7		|___			|_	
	8		|			|	
	9	p	|		q	|	
	10		|			|	
ARIMA (0, 1, 0) (a)	1		|_____			|_____	
	2		|_____			|	
	3		|_____			|	
	4		|_____			|	
	5		|_____			|	
	6		|_____			|	
	7		|_____			|	
	8		|_____			|	
	9		|_____			|	
	10		|			|	
ARIMA (0, 1, 0) (b)	1		|_____			|_____	
	2		|_____			|	
	3		|____			|	
	4		|__			|	
	5		__|			|	
	6		____|			|	
	7		____|			|	
	8		__|			|	
	9		|__			|	
	10		|____			|	
	11		|____			|	
	12		|__			|	

2.3.3 Trend component and stationary

In order to establish whether a given series contains autocorrelation, it is necessary to explore whether the series is stationary. This is an important concept in time series analysis. A time series is stationary if

- It exhibits a reversion around a constant long-run mean;
- It has a finite variance that is time invariant; and

- It has a theoretical correlogram that diminishes as the lag length increases.[195]

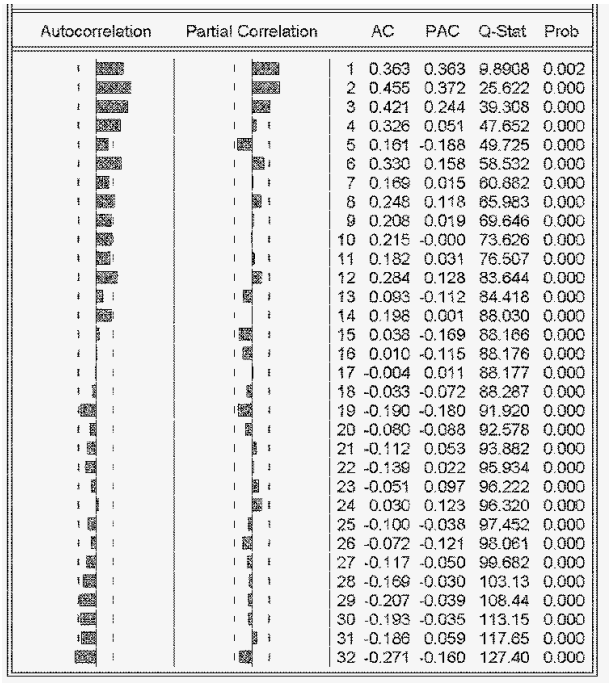
In other words the properties are stable over time.

Series containing such unit roots are classified as difference stationary. Series with trend and without a unit root are classified as trend stationary and can be analysed using generalised regression methods.

Stationary series vary around a constant mean level, either increasing or decreasing systematically over time with a constant variant. Non-stationary series have systemic trends such as linear or quadratic. A non stationary series that can be made stationary by differencing is called "non-stationary in the homogenous sense". [198]

Figures 2.1.a and 2.1.b show examples of correlograms and raw graph for non-stationary series 1 and stationary series 2.

Figure 2.1.a: Example of correlogram and raw data graph for a non-stationary series, Series01



Autocorrelation	Partial Correlation		AC	PAC	Q-Stat	Prob
		1	0.363	0.363	9.8908	0.002
		2	0.455	0.372	25.622	0.000
		3	0.421	0.244	39.308	0.000
		4	0.326	0.051	47.652	0.000
		5	0.161	-0.188	49.725	0.000
		6	0.330	0.158	58.532	0.000
		7	0.169	0.015	60.882	0.000
		8	0.248	0.118	65.983	0.000
		9	0.208	0.019	69.646	0.000
		10	0.215	-0.000	73.626	0.000
		11	0.182	0.031	76.507	0.000
		12	0.284	0.128	83.644	0.000
		13	0.093	-0.112	84.418	0.000
		14	0.198	0.001	88.030	0.000
		15	0.038	-0.169	88.166	0.000
		16	0.010	-0.115	88.176	0.000
		17	-0.004	0.011	88.177	0.000
		18	-0.033	-0.072	88.287	0.000
		19	-0.190	-0.180	91.920	0.000
		20	-0.080	-0.088	92.578	0.000
		21	-0.112	0.053	93.882	0.000
		22	-0.139	0.022	95.934	0.000
		23	-0.051	0.097	96.222	0.000
		24	0.030	0.123	96.320	0.000
		25	-0.100	-0.038	97.452	0.000
		26	-0.072	-0.121	98.061	0.000
		27	-0.117	-0.050	99.682	0.000
		28	-0.169	-0.030	103.13	0.000
		29	-0.207	-0.039	108.44	0.000
		30	-0.193	-0.035	113.15	0.000
		31	-0.186	0.059	117.65	0.000
		32	-0.271	-0.160	127.40	0.000

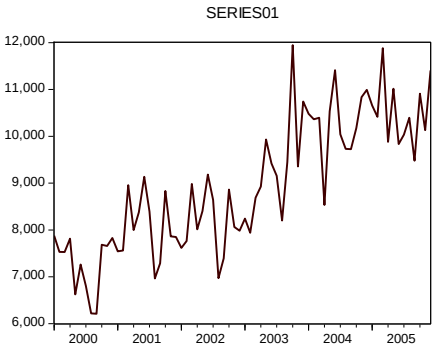
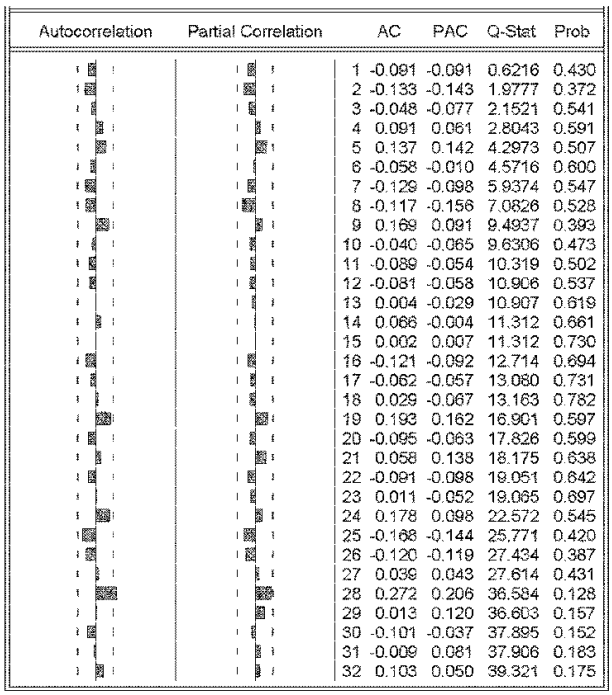
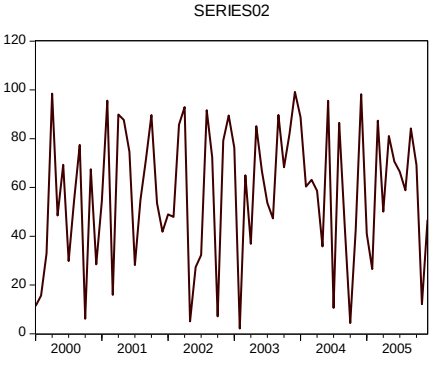


Figure 2.1.b: Example of correlogram and raw data graph for a stationary series, Series02



Autocorrelation	Partial Correlation		AC	PAC	Q-Stat	Prob
		1	-0.091	-0.091	0.6216	0.430
		2	-0.133	-0.143	1.9777	0.372
		3	-0.048	-0.077	2.1521	0.541
		4	0.091	0.061	2.8043	0.591
		5	0.137	0.142	4.2973	0.507
		6	-0.058	-0.010	4.5716	0.600
		7	-0.129	-0.098	5.9374	0.547
		8	-0.117	-0.156	7.0826	0.528
		9	0.169	0.091	9.4937	0.393
		10	-0.040	-0.065	9.6306	0.473
		11	-0.089	-0.054	10.319	0.502
		12	-0.081	-0.058	10.906	0.537
		13	0.004	-0.029	10.907	0.619
		14	0.066	-0.004	11.312	0.661
		15	0.002	0.007	11.312	0.730
		16	-0.121	-0.092	12.714	0.694
		17	-0.062	-0.057	13.080	0.731
		18	0.029	-0.067	13.163	0.782
		19	0.193	0.162	16.901	0.597
		20	-0.095	-0.063	17.826	0.599
		21	0.058	0.138	18.175	0.638
		22	-0.091	-0.098	19.051	0.642
		23	0.011	-0.052	19.065	0.697
		24	0.178	0.098	22.572	0.545
		25	-0.168	-0.144	25.771	0.420
		26	-0.120	-0.119	27.434	0.387
		27	0.039	0.043	27.614	0.431
		28	0.272	0.206	36.584	0.128
		29	0.013	0.120	36.603	0.157
		30	-0.101	-0.037	37.895	0.152
		31	-0.009	0.081	37.906	0.183
		32	0.103	0.050	39.321	0.175



There are two general approaches to achieve this: 1) differencing by subtracting the value of each data point from previous data point 2) de-trending the series using a regression approach. The two relevant features in plot of a time series are the central tendency and dispersion. If the mean is changing, the trend is removed by differencing. After removing the trend the series are expected to be stationary with respect to central tendency. If the variability is changing, the process may be made stationary by logarithmic transformation. If after transformation the variability does not improve, untransformed series are used in future analyses. [200]

The visual tests for whether a series is stationary are based on the correlogram. For a stationary series, the correlogram will die out quickly as the lag length increases, while in a non-stationary series the correlogram will not die out quickly. However this might be imprecise if confused with the examination of correlogram for autocorrelation. [194] The best way is to use a formal statistical test for stationarity.

2.3.4. Statistical tests for unit root

Dickey- Fuller test

The Dickey-Fuller [201] test for whether a time series is stationary is simply the normal *t*-test on coefficients of lagged dependent variable y_{t-1}. This test does not have a conventional *t* distribution and so we must use critical values which were originally calculated by Dickey and Fuller. A limitation of this test is when a series contains a major break such as change in level or slope. Another limitation is that when the null hypothesis of a unit root is rejected it does not necessarily mean that the error term is a result of a white noise, and it may be affected by autocorrelation.[195] Enders showed that the Dickey-Fuller test has limited power and suggested adopting a more liberal alpha

(e.g. P<0.1 rather than than P<0.05) in order to avoid differencing in the series which are not in fact difference stationary in nature. [197]

Augmented Dickey-Fuller test (ADF)

Since the error term is unlikely to be the white noise, Dickey and Fuller extended their test procedure suggesting an augmented version of the test which includes extra lag terms of the dependent variable in order to eliminate autocorrelation. The lag length of those extra terms is either determined by the Akaike Information Criterion (AIC) or Schwartz Bayesian Criterion (SBC), or more usually by the lag length necessary to whiten the residuals.[195] The Augmented Dickey-Fuller test (ADF) includes extra lag terms of dependent variable in regression to eliminate autocorrelation in detecting white noise.

The Phillips-Perron Test (PP)

While the ADF test corrects for higher order of serial autocorrelation, the Philips-Perron (PP) test makes a modification that takes into account the less restrictive nature of the error process. Philips and Perron 202 further developed the ADF test.

The distribution theory supporting the Dickey-Fuller tests is based on the assumption that the error terms are statistically independent and have a constant variance. So, when using the ADF methodology we have to make sure that the error terms are uncorrelated and that they really have a constant variance. Phillips and Perron (1998) developed a generalization of the ADF test procedure that requires less restrictive assumptions. While the ADF test corrects for higher order series correlation by adding lagged differenced terms, the PP test make a correction to the t statistics of the coefficient γ from AR(1) regression to account for the serial correlation in e_t. So, the PP statistics

are modifications to the ADF test that take into account the less restrictive nature of the error process. The asymptomatic distribution of the PP *t* test statistics is the same as the ADF *t* statistics and therefore the Mackinnon (1991) critical values are still applicable. As with the ADF test, the PP test can be performed with the inclusion of a constant, a constant and linear trend, or neither in the test regression. [195]

The Box-Jenkins approach is a series of re-estimating and diagnosis to capture the best possible ACF and PACF of the residuals. This approach is conceptualised as (p, d, q) where p represents the order of AR and q the order of MA (if present) and d the differencing order. This approach is called ARIMA (p, d,q) or Autoregressive Integrated Moving Average. The autoregressive element, p, is persisting effect of preceding scores. The integrated element, d, represents trend in time points, and moving average element, q, is the persisting effect of preceding random shocks. When the value of p, d, or q is zero, the element is not needed in the model. The set of more general ARMA (Autoregressive Moving Average) elements that utilises the AR and MA but can use different approaches to achieve a non-stationary in differencing the model. [199]

2.3.5 Autoregressive Process

The autoregressive component is the memory of the process for preceding observation. Most time series consist of elements that are serially dependent on the consecutive element or coefficients called an autoregressive process, memory of elements. In this process a coefficient or a set of coefficients describe the consecutive elements. In other words each component is made up of a random error component and a linear combination of prior observations. One approach to autocorrelation is the autoregressive process.[203] Autoregressive process of order P for a stationary time series Y is theorised in the following equation[203]

$Y_t = C + \Phi Yt_{-1} + \Phi Y_{t-p} + ... + \Phi_p Y_{t-p} + a_t$ (2.1)

In which the value of Y in a given time has constant C, a random shock or error component of a_t and the components of Y values at previous lag with P order. Therefore a first order autoregressive process would be:

$Y_t = C + \Phi Y_{t-1} + a_t$ (1.8) (2.2)

It implies that the value of Y at a given time t is dependent on a random component defined by the parameter Φ. If the definite value of coefficient Φ is greater or equal to one, there is a random walk and the series is not stationary. [196]

For an autoregressive order of two the coefficients Φ_1 and Φ_2 must meet the following condition: $\Phi_1 \mp \Phi_2 < 1$. These are called bounds of stationary for an autoregressive parameter(s). [198]

2.3.6 Moving Average Process

The moving average component is the memory of the process for the preceding random shock. In order to eliminate noise of individual observations, in time series analysis we can average a number of observations around time t to get the measure of central tendency. Moving average cancels positive and negative shocks, so taking an average should normally reduce any idiosyncratic noise in the series. [199]

If X_t denotes the level of our series at time *t*, the moving average M_t is defined as[198]

$$Mt = \frac{1}{F+L+1} \sum_{I=-L}^{i=F} Xt + i \quad (2.3)$$

where *L* denotes the number of lagged terms to include in the average and *F* denotes the number of leading terms to include. The number of lagged terms depends on the periodicity of data. Commonly the number of terms chosen to include in a moving

average is the number of time periods in a year. For quarterly data four terms are used, and for monthly data twelve terms are used. Nonetheless a four-period moving average cannot smooth out fluctuations that occur over an entire year. On the other hand, a twelve-period moving average is based on data that span an entire year, resulting in an average that is not influenced by seasonal factors. This doesn't mean that analyses should only use monthly data. In fact, if we want to make the seasonal fluctuations visible, we can use three or four-monthly data to do this. The number of available observations is also important, so with a low number of data points we tend to use lower MA process to avoid having too few data points in final analysis.[197]

When q is 1, there is a relationship between the current time point and the random shock at lag 1. It is also possible that each element in the series is dependent on past error terms which cannot be accounted in autoregressive process. In other words the each time point is made up of a random error component (random shock) and a linear combination of prior error components (random shocks). [195, 197]

The MA process equation can be inverted (rewritten) to AR process, a duality between MA and AR.[196] This can happen when the MA parameters follows a process called invertibility; otherwise the series are not stationary. If *q* is the order of moving average process:

$$Y_t = C + \theta_1 Y_{t-1} + \ldots + \theta q Y_{t-q} \quad (2.4)$$

Therefore for a first order MA process would be:

$$Y_t = C + \theta Y_{t-1} \quad (2.5)$$

For a first order moving average process the coefficients, θ, must be between -1 and 1 and for second order it must meet the following condition $\theta_1 \pm \theta_2 < 1$. These are called bounds of invertibility.[198]

2.3.7 Seasonality in time series

The nature of time series has a function of periodicity. The outcome of interest may vary on a seasonal basis. Monthly data with a seasonal component exhibit seasonal effects at lag 12 while quarterly data show the seasonality at lag 4. When time series contain seasonality the ACF and PACF show significant spikes at multiples of lags equal to periodicity. For example in monthly series with seasonal variation the ACF plot shows spikes at lags 12, 24, 36 that die out slowly. When a series does not contain a seasonal unit root, the magnitude of the autoregressive parameters decrease approximately exponentially. There are various approaches to detect and test for seasonality, and to include seasonality in time series. Detection and inclusion of a seasonal component are implemented in time series analysis methods with ARIMA, ARMA, and dynamic regression of time series because seasonality induces autoregressive and moving average process. Here, seasonal component and two methods of adjusting for seasonality are briefly described.[199]

Two basic components of time series are trend and seasonality. The seasonal component could interact with trend components either in a multiplicative or in an additive way.

2.3.8 Time domain approach for seasonality

For a time domain approach, used in additive seasonality [199], we can apply deterministic seasonal dummies or adopt a stochastic approach to estimate seasonal autocorrelation terms. Seasonal variations can be easily examined by the use of dummy variables in

regression. In a stochastic seasonal approach the autocorrelated error terms at a given seasonal lag are incorporated in the model. [195, 199]

2.3.9 Seasonal decomposition

When seasonal component exists, seasonal decomposition is way of decomposing a series into its components; trend and seasonality in either an additive or multiplicative interaction. This method can therefore remove the seasonality component, and is suitable for when the analyst is interested in trend or wants to forecast. [204] The method is particularly useful when the seasonal component is multiplicative and the study is an interrupted time series analysis. In this case, the decomposition based approach can be used to remove seasonality before the intervention analysis. Adjusting for seasonality by seasonal decomposition approach method is built-in in statistical packages.

2.3.10 Multivariate Time Series

Multivariate time series is analysis of the relationship between two or more time series. Other terms are also used as cross-correlation function, transfer function models, models with input series, and dynamic regression.[205]

2.4 Other statistical concerns in time series analysis [194, 195]

2.4.1 Collinearity

Collinearity arises when a predictor variable is highly correlated with another predictor variable. The presence of collinearity may bias the regression estimates, variance estimates and the test statistics and the test statistics and *P* values. An approach to test the collinearity is regressing predictor variables with one another, which is called a tolerance test.

2.4.2 Outliers

Outliers are very common in inconsistent time series. They can greatly affect the results, and should be dealt with. Checking the original data, deleting outliers and replacing the observations with imputed values, and using dummy variables are several measures to deal with outliers. There is no single best way to deal with outliers and so in the series these kind of time points should be labelled as outliers.[198] An outlier time point may indicate an important change such as an intervention, in which case it should be modelled by an interrupted time series design.

2.4.3 Nonlinear trend

It is possible that while the data do not contain a unit root, the nature of the trend is not linear, for example increasing or decreasing in a quadratic character. In this case applying a linear trend term to the model will be misleading. One approach is applying polynomial terms where appropriate.

2.4.4 Model Selection Criteria[195, 198]

The random shock that happens in the series is assumed to be independent and normally distributed. Contingencies among errors over time are a part of model identification and estimation. If the model is powerful then all serial contingencies are removed so that the final model is left with random distribution of errors. This should be reflected by the residual error having mean zero and homogeneity of variance. When the residuals are not normally distributed, then square root, logarithmic, or inverse transformations are appropriate measures. In the final model there should be no remaining autocorrelations at various lags.[205]

Statistical packages report R-Squared, adjusted R-squared that help in this stage. Two other important outputs are AIC (Akiake's Information Criterion) and SBC (Schwarz's

Bayesian Criterion). Ideally, we select the model that minimises these statistics, as compared to alternative specifications.[195]

In summary, in analysis of time series the following steps are suggested:

1- Check for normality of data

2- Examination of time plots, ACF and PACF

3- Establish whether the series are stationary

4- Check and account for autocorrelation, and seasonal adjustments

5- Fit the model

6- Examine the residuals, and other tests for model comparison.

7- Test the plausibility of alternative models and asses the relevant test results and outputs.

2.5 Interrupted Time Series Analysis (ITSA)

Analysis of a time series with an intervention (an interrupted time series) examines a time series before and after the intervention. This method is the strongest quasi-experimental design to evaluate longitudinal effects of such time delimited interventions.[206] Interrupted time series analysis design is widely used to evaluate the effects of one or more events or intervention retrospectively or prospectively. Statistical methods are piecewise or segmented regression, and ARIMA and ARMA based models. The statistical tests, precautions, and procedure are mainly the same as time series analysis. Segmented regression analysis is appropriate for studying the impact of interventions that constitute a natural experiment (eg where researchers examine the effect of a policy change) or quasi-experiment (eg where researchers themselves create an intervention). It requires data on continuous or counted outcome measures,

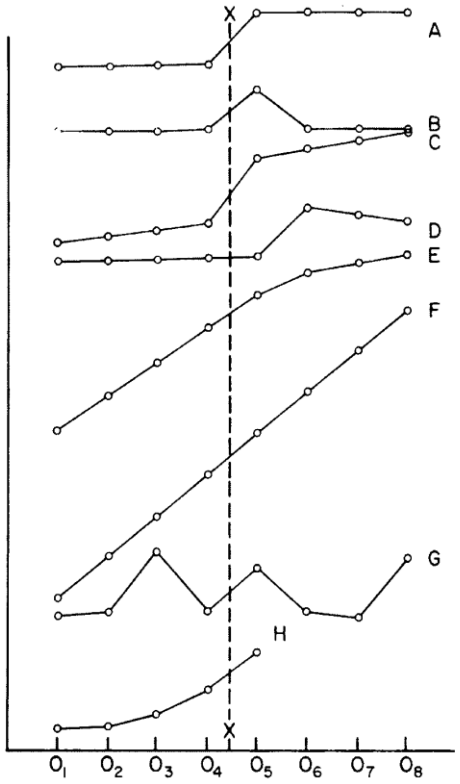
summarised at regular, evenly spaced intervals.[206] These designs are also suitable when a randomised control trial is not feasible.

The effects produced by interventions differ in both the onset (abrupt or gradual) and duration (permanent or temporary). In quasi-experiment designs it is more likely that the intervention lasts for a long time. Because there are two levels of duration and two levels of onset, there are four possible combinations of effects, but gradual onset, temporary effects occur rarely and require curve fitting.[198]

Segmented regression analysis of interrupted time series allows the assessment, in statistical term, of how much an intervention changed an outcome of interest, immediately and over time; instantly or with delay; transiently or long term; and whether factors other than the intervention could explain the change. The choice of the beginning and end of each segment depends on the beginning and end of the intervention, with the possible addition of some pre-specified lag time to allow the intervention to take effect. [206] Segmented regression analysis uses least squares estimation of parameters. This method is appropriate when the response variable has a linear trend over a certain range of independent variable (time), followed by another linear trend over a succeeding range.[207]

Campbell and Stanley[208] identified eight patterns of time series data that may result from a change as shown in figure 2.2. Series H exhibits a polynomial pattern. Series B represents a temporary effect. From the remaining models A, C, D, E, F and G can be handled by segmented regression while case H would require a polynomial or other type of regression model, as a linear trend is not appropriate. [207]

Figure 2.2: Patterns of time series interrupted with an intervention adopted from Gillings et al.[207]



Outcomes of an intervention, using ARIMA, ARMA or segmented regression, are expressed by three measures; change in level and change in slope after the intervention and the intervention effect size if nothing had happened. This is fitted in models using dummies for each change or intervention point.

The graphical illustration of interrupted time series with segmented regression is presented in Figure 2.3 adopted from chapter 3 of this thesis. The regression model in case of one change without lag time is:

$$Y = B_0 + (B_1 \times T_t) + \left(B_2 \times T_i\right) + \left(B_3 \times T_{ai}\right) + e_t \quad (2.6)$$

where, T series are time variables. T_t is a continuous variable starting from 1 to the last time point in series. T_i is a dummy variable coded zero for pre-intervention and 1 for

post-intervention time points. The term T_{ai} refers to time after the intervention. It is a continuous variable counting number of time points after the intervention and coded zero for pre-intervention time points.

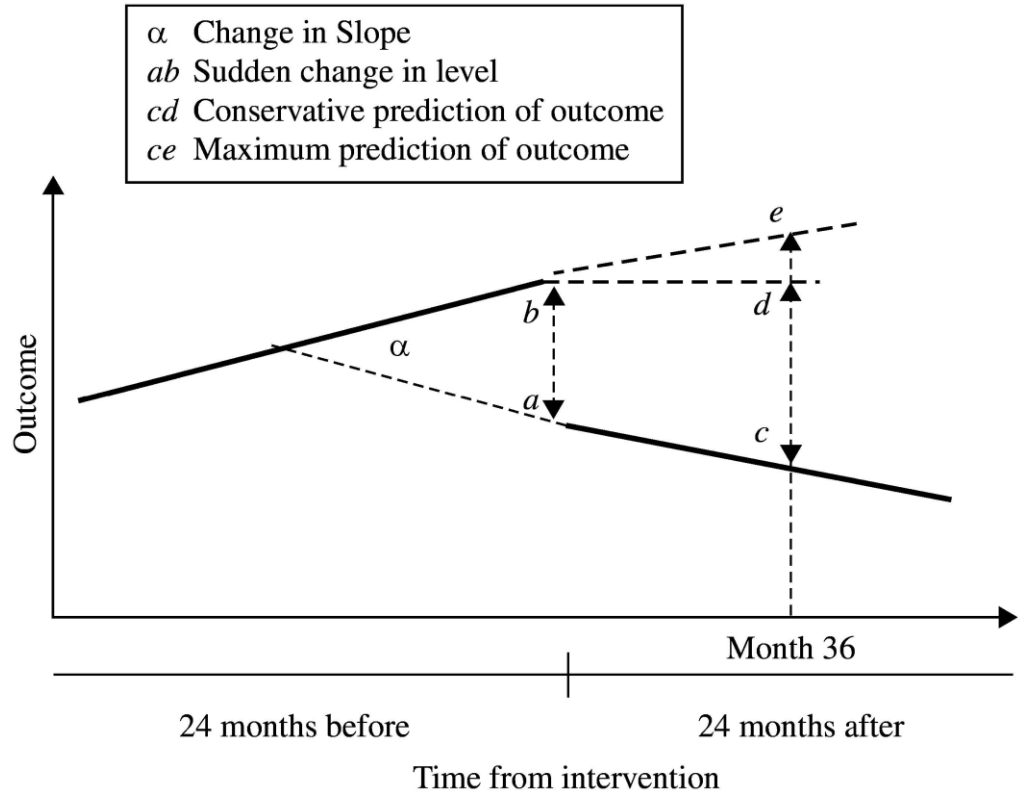
In this model B_0 estimates the level of outcome at time zero. B_1 is the slope of the pre-intervention segment and estimates the mean change in outcome per month before the intervention. The coefficient B_2 estimates the level of change immediately after the intervention. B_3 estimates change in slope after the intervention (α in Figure 2.3) and represents the monthly mean of the outcome variable. The sum of $B_2 + B_3$ is the slope of the post-intervention segment. The error term e_t represents normally distributed random error and an error term at time *t* that may be correlated to errors at preceding or subsequent time points.

Estimation of intervention effect had the intervention not occurred for time T_n where *n* is a given time after the intervention is expressed in the following equation (*ce* in Figure 2.3) :

$$Intervention\ effect\ T_n = (B_2 + B_3) \times n \quad (2.7)$$

Change in level (*ab* in Figure 2.3) is the size of the immediate intervention effect, and change in slope represents the sustainability of the intervention effect.

Figure 2.3: A model for interrupted time series analysis with segmented regression [209]



The single most important thing to remember about time-series experiments is that they require long baseline periods to establish whether the process is stationary or non-stationary. In general it is difficult to say exactly how long a baseline must be for a time series experiment to reliably establish this. It is found that time series of observations of a single individual are often stationary, particularly if you discard the first few points during which the subject may be acclimatising to the equipment or observation procedure. On the other hand, time series based on large groups of persons - like classrooms, cities, or the population of an entire nation - are often non-stationary. [198, 210]

Sample size

A sufficient number of time points before and after the intervention is needed to conduct segmented regression analysis. A general recommendation is for 12 data points before and 12 data points after the intervention, although this number is not based on estimates of power. Rather, with 24 monthly measures, the analyst can adequately evaluate the presence of, and account for seasonal variation (Figure 2.3). There also needs to be a sufficient number of observations at each data point. A minimum of 100 is desirable at each data point of the time series to achieve an acceptable level of variability of the estimate at each time point. [206, 208] Additional change points may also serve to control for changes in the series that are not of primary interest but may influence the results. Examples include discontinuities in the series at time points other than that of the intervention because of administrative changes and lagged or multi-period interventions.[206, 208]

It is important to account for lags in impact (the delayed effect of an intervention) and multi-period interventions in the analysis to avoid incorrect specification of intervention effects. To model these effects, one can exclude from the analysis outcome values that occur during the lag or the period 'during the intervention'. Alternatively, with enough data points, one can model this period as a separate segment.

A major strength of segmented regression analysis is that in the absence of a control group the pre-intervention segment can reserve as a control group and baseline measurement. [206, 207]

ITS designs are subject to threats to internal validity that are related to history (such as seasonality) that influence the dependent variable, maturation bias where there is a pattern of improvement in the experimental group prior to the intervention, and

instrumentation bias. For example changes in the way records are kept or the way the outcomes are measured and selection bias which could cause a differential drop out in the experimental group.[211]

2.5.1 Quality Criteria for ITSA

Ramsay *et al.* [212] developed the following quality criteria checklist from two sources, the Cochrane Effective Practice and Organisation of Care (EPOC) data collection list[211] and classification of threats to validity identified by Campbell and Stanley.[208] High quality ITSA tends to have the following features:

1- Intervention occurred independent from other changes over time

2- Intervention was unlikely to affect data collection

3- The primary outcome was reliable and assessed blindly or was measured objectively

4- The shape of the intervention effect was pre-specified

5- A rational for number and spacing of data points was described

6- The study was analysed appropriately using time series analysis.

It is possible that other events are responsible for the change after the intervention and for this reason it is preferable to employ a control group.[206, 207] However, without having a control group if the dataset is large enough to give enough power it is possible to model more than one structural event.

CHAPTER THREE: OUTCOMES OF AN INTERVENTION TO IMPROVE HOSPITAL ANTIBIOTIC PRESCRIBING IN DUNDEE: INTERRUPTED TIME SERIES WITH SEGMENTED REGRESSION ANALYSIS

3.1 Background

NHS Tayside has had a leading role in the UK for initiating prudent antibiotic prescribing through a series of audits, quality improvement projects and innovative service developments in primary and secondary care over the last two decades.[213-218] Nonetheless, there was a need for novel methods in evaluating interventions, implementing the new Drug Utilisation Review (DUR) methods to incorporate them into institutional goals to monitor, control and prevent inappropriate use of antibiotics.[219, 220] This chapter consists of evaluation and management of antibiotic prescribing through evaluation of the Alert Antibiotic Intervention programme.

3.2 Introduction

In 2002, the Scottish Executive Antimicrobial Resistance Steering Group was established to gain commitment to a co-ordinated, focused approach at the local, national and international levels for prudent antimicrobial use in humans and set the surveillance of antimicrobial use and resistance as one of the key elements.[107]

In UK 62% of the hospitals have a policy for antibiotic therapy but few had information systems for easy assessment of practice. [219] On the other hand, across the UK, the selection of indicators in studies to measure and monitor drug use especially in hospitals was very different so that it was difficult to compare data over time or within different regions, therefore, a new measure based on standard daily dosages is needed [24].

These units are not without their problems, but they avoid many of the deficiencies of the item. The DDD adjusted for bed occupancy (DDD/100 bed-days) is a practical tool for measuring drug use in hospitals. Despite the implementation of this indicator across Europe during the last two decades, it was rarely used in drug utilisation studies in the UK.

At NHS Tayside Acute Services Division (ASD) Tayside Medicines Unit (TMU) used reported the annual drug usage and drug expenditure information but the data took time to gather because this involved manual addition of data on different formulations of the same drug. Reports generated since 1999 show rates of expenditure by therapeutic class (e.g. anti-infectives) but only provide limited data about the utilisation of specific drugs.

Furthermore, annual changes in the trend of anti-microbial prescribing were only identified when financial year end budget reports were produced. It was difficult at that stage to identify why certain increases in expenditure or usage occurred or to effect any intervention that might have an impact on this trend. A system allowing the prospective monitoring of prescribing practices and regular publication of usage figures should allow real-time feedback to prescribers, a much tighter management of these drugs and hopefully trigger more judicious prescribing during periods when usage appears to be getting out of control. There could also be the potential for significant cost savings.

In 2000, the Antibiotic Subcommittee of Tayside ASD devised an Alert Antibiotic Policy to reduce inappropriate use of key antibiotics, targeted because they should be reserved for infections caused by organisms that are resistant to the first line antimicrobials. I conducted the first evaluation of this intervention before the work reported in this thesis, and relied on analysis of the records of patients prescribed an Alert Antibiotic completed by the ward pharmacists. The number of Alert antibiotics

records declined from 41 per month in the first year to 25 per month in the second year. The proportion of prescriptions that were appropriate was similar in the 2 years; 83% and 84%. Two fundamental problems with using patient records as a measure of outcome of the Alert Antibiotics Policy were identified. Firstly, patient records are not an objective measurement of outcome. Outcome measures such as appropriateness of care should be based on a questionnaire with known reliability and validity. Moreover, outcome measures that are obtained by chart extraction or collected by an individual require two or more rates with at least 90% agreement or kappa greater than or equal to 0.8. [221] Secondly, patient records provided no information about practice before the start of the intervention and consequently it was impossible to say whether the reduction in the number of records was the result of the impact of the intervention or simply a decline in the return of records by the pharmacists.[220-222]

In this study routine data from the pharmacy stock control computer used to evaluate the intervention with an Interrupted Time Series Analysis (ITSA), in which a series of observations over time is interrupted by an intervention or treatment. [206, 223]

3.3 Aims

- What is the impact of an Alert Antibiotic Policy on the use of antibiotics reserved for second line treatment of resistance organisms?
- What is the cost of designing and implementing of the policy and to what extent are these costs offset by savings in drug costs?

3.4 Methods

3.4.1 Setting

The intervention, an Alert Antibiotic Policy, was implemented in Ninewells Hospital which is a tertiary university hospital in Tayside, Scotland.

3.4.2 Design of the Alert Antibiotic Intervention

The design of intervention to change prescribing was based on evidence about changing professional behaviour in the Effective Practice and Organization of Care (EPOC) section of the Cochrane Database. [224-229] From this evidence and an earlier systematic review of the literature on behaviour change [230] three key elements for the intervention were identified: development, dissemination and implementation. The Tayside Antibiotic Subcommittee developed the Alert Antibiotics Policy, the committee is multi-disciplinary, chaired by a surgeon and includes representation from junior staff and the clinical groups in addition to local opinion leaders. The committee's dissemination strategy was targeted at specific professionals and clinical teams via the clinical pharmacists. The implementation strategy used immediate, concurrent feedback of information to the prescribers, who were contacted by the clinical pharmacist while their patient was still being treated.

The Policy targeted the following drugs (Alert Antibiotics):

(i) Carbapenems: Imipenem and Meropenem

(ii) Glycopeptides: Teicoplanin and Vancomycin

(iii) Intravenous (IV) Amphotericin

(iv) Ciprofloxacin (IV)

(v) Linezolid (IV and oral)

(vi) Piperacillin-Tazobactam (Tazocin)

(vii) Third generation cephalosporins: Ceftriaxone, Cefotaxime and Ceftazidime.

In August 2000, the intervention was put into effect in up to 40 medical and surgical wards of Ninewells Hospital, excluding Haematology and Paediatrics. Haematology

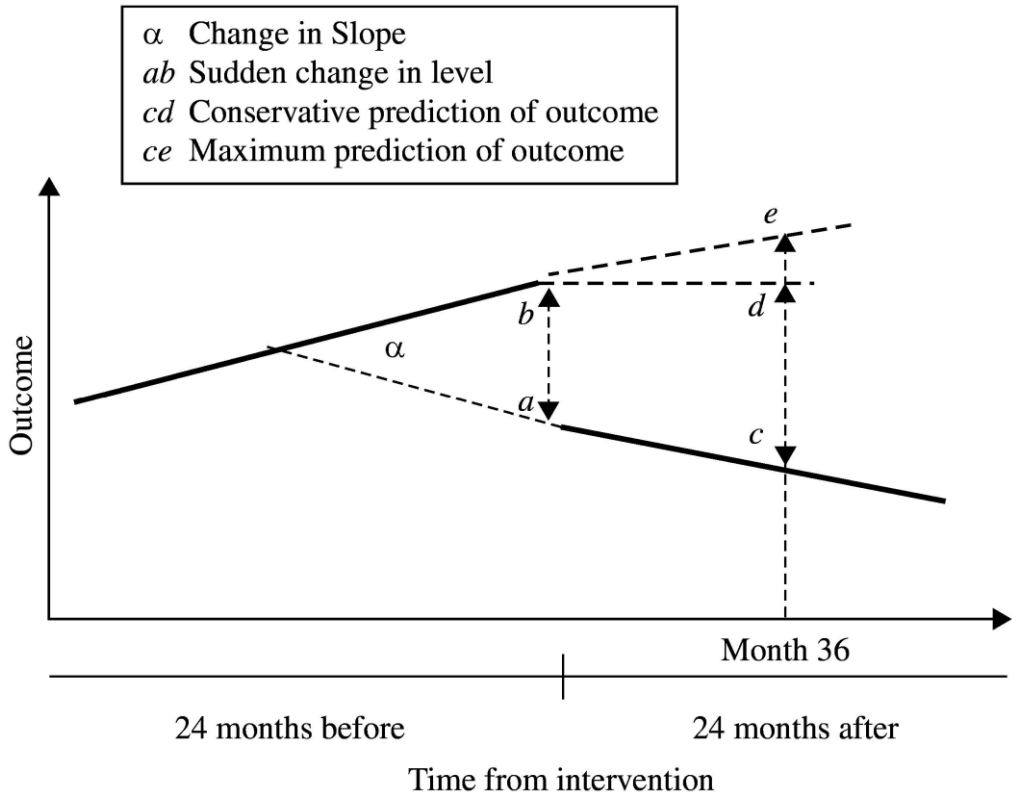
and Paediatrics were excluded because these wards had their own policies for prescribing Alert antibiotics. Guidelines for prescribing use were evidence-based and agreed locally with the clinicians. Clinical pharmacists were asked to identify prescribing of the Alert Antibiotics by the medical staff in their wards and confirm that their use was in line with the agreed guidelines. If not, the pharmacists asked medical staff to review their choice of antibiotic and advised them to contact microbiology or infectious diseases physicians for advice if necessary.

3.4.3 Evaluation of the intervention

Segmented regression analysis of Interrupted Time Series (ITS) design allows us to assess, in statistical terms, how much an intervention changed an outcome of interest, both immediately and over time. When a separate control group is not available, analysis of the outcome of interest in the study group does not allow for other events that may have influenced the outcome if sufficient data are not available. Nonetheless, the level and trend of the pre-intervention segment serves as a control for the post-intervention segment in single group time series, still addresses important threats to internal validity and represents a methodologically acceptable design for measuring the impact of interventions. Accounting for seasonally correlated errors usually requires at least 24 monthly data points. [206] Detailed description of statistical method used in this chapter is previously described in Chapter 2 of this thesis , time series analysis and interrupted time series. Figure 3.1 is the graphic illustration of outcome measurements in segmented regression of interrupted time series analysis. Three outcomes in the ITS analysis are: first, change in level immediately after the intervention (*ab)*; secondly, a difference between pre-intervention and post-intervention slopes (α); and third, the estimation of monthly average intervention effects after the intervention (*ce*). [206, 223, 231] In addition to the main outcomes of ITS analysis a further more conservative analysis

was performed. For this, no increase was assumed after the intervention and the difference with the mean observed use and cost after the intervention calculated. In Figure 3.1 conservative estimation is *cd* which is equal to *ce-dc*.

Figure 3.1 Graphic illustration of interrupted time series analysis and measuring the outcomes according to the best-fitted lines for data points before and after the intervention.



Usage and cost data were collected and analysed for 2 years before and 2 years after the intervention in order to minimise the effect of seasonal variation. Data were adjusted for autocorrelation. For statistical analysis, autoregressive time series analysis method was implemented using SPSS® software. (SPSS Inc. 2002. SPSS Base 11 for Windows User's Guide. SPSS Inc., Chicago IL)

Linezolid and Imipenem were excluded from the ITS analysis because there were less than 12 monthly data points before the intervention. The level of significance was 0.05.

3.4.4 Data collection

After evaluation of the intervention using analysis of patient records and the related shortcomings of this method [221], pharmacy stock data were used. During the 4 year period of analysis, the hospital pharmacy did not implement a restriction policy on dispensing the Alert Antibiotics and therefore the pharmacy data provided the best available independent indicator for evaluating the intervention. The impact of the intervention on antibiotic prescribing was analysed using data about the quantity of Alert Antibiotics dispensed to the hospital wards per month for 2 years before and after the start of the intervention. A program was written to collate data relating to the dispensing of all dosage forms of the relevant drugs and conversion of the total grams dispensed were converted into Defined Daily Doses (DDD). The DDD as defined by the WHO Collaborating Centre for Drug Statistics Methodology (WHO CC) as 'the assumed average dose per day for a drug used on its main indication in adults.[232, 233] The DDDs were adjusted for bed occupancy and is presented as DDD/1 00 bed-days.

3.4.5 Cost analysis

As the average price of Alert Antibiotics dosage forms might have decreased during the post-intervention period, the average price of each dosage form over the 4 year period of the study was calculated and used to eliminate any effect of fluctuation in drug prices. The final results were measured with £/bed-days/month but are presented in £/month.

The total cost of the Alert Antibiotic Policy and clinical pharmacy intervention was calculated by measuring the time required for consultation, completion of the records, data entry and interpretation. The time required for additional meetings of the Antibiotic Policy Committee was quantified and additional consumable materials were recorded.

Time was costed using the average hourly rate for each staff grade in each of the years of the intervention, including employer's contributions and national insurance.

3.5 Results

Before the intervention, both use and cost of Alert Antibiotics were on the increase but after the intervention both use and cost declined – as shown in Figures 3.2 and 3.3.

Figure 3.2: Changes in use of alert antibiotics 24 months before and after the intervention.

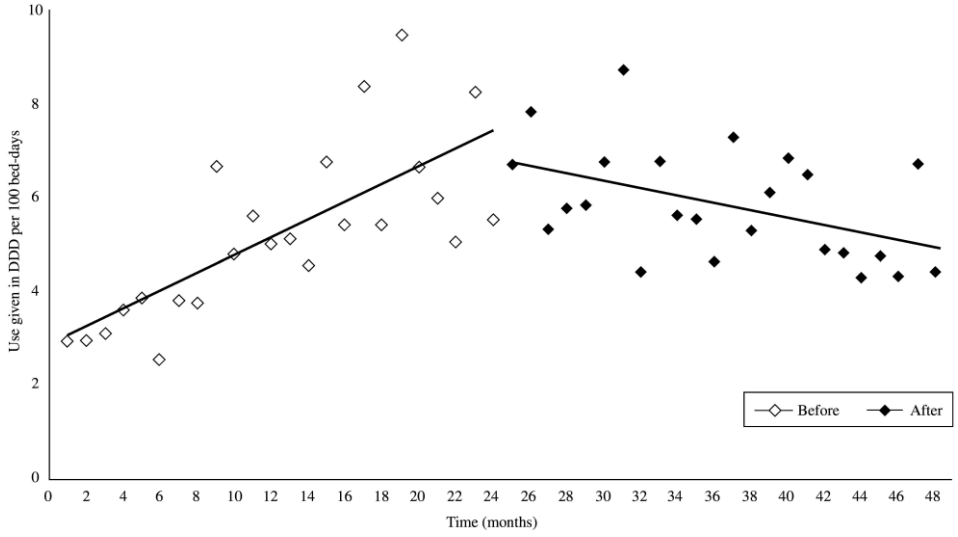
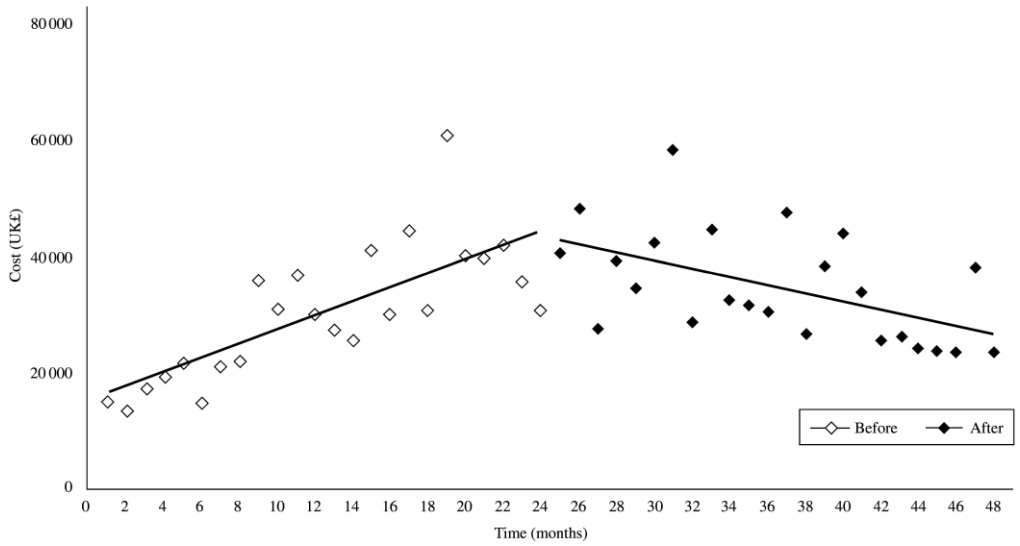


Figure 3.3 Changes in cost of Alert antibiotics 24 months before and after the intervention.



The intervention was associated with a significant change in the level of use of Teicoplanin and Ceftazidime, but there was no significant change in the level for all Alert Antibiotics combined (Table 3.1). There was a significant change in the slope so that overall use of all Alert Antibiotics decreased by 0.27 DDD/100 bed-days per month (95% CI 0.19—0.34, P < 0.0001). There were also significant decreases in the slope for Amphotericin, Ciprofloxacin, Piperacillin-Tazobactam, Teicoplanin, and Vancomycin. The slope of Ceftriaxone usage increased significantly but there were no significant changes in slope for use of Ceftazidime, Meropenem or Cefotaxime. The results of statistical analysis of changes in cost were similar to change in use as shown in Table 3.2 The analysis of change in the slope showed a reduction in cost of Alert Antibiotics by £1,908 per month in the two years after the intervention (95% CI £1,238- £ 2,578: P<0.0001).

Over 2 years, it was estimated that the Alert Antibiotic Policy reduced use by an average of 4.03 DDD/100 bed-days per month (Table 3.1) and reduced cost by an

average of £23,852 per month (Table 3.2). The estimated use and cost of each individual drug was reduced, with the exception of Ceftriaxone, for which use and cost increased (Tables 3.1 and 3.2). The average reduction in use was greatest for Teicoplanin (1.02 DDD/l00 bed-days per month), Piperacillin-Tazobactam (0.80), and Vancomycin (0.78). The average reduction in monthly cost was greatest for Amphotericin (£8,075), Piperacillin-Tazobactam (£6,800) and Teicoplanin (£3,173). A more conservative estimate of effect size was calculated from the difference between the post-intervention line and the last point on the pre-intervention line (Figure 3.1). This conservative estimate was a decrease in total use by 1.60 DDD/l00 bed-days/month (95% CI 1.9-2.1, P <0.0001) (Table 3.1) and a decrease in cost by £9,590/month (95% CI £5,554- £ 13,626, P <0.0001) (Table 3.2).

Table 3.1: Change in use of Alert Antibiotics after the intervention

	Change in level				Change in slope				Maximum estimation of reduction	Conservative estimation of reduction
Antibiotic	mean	LCI	UCI	*P* value	mean	LCI	UCI	*P* value	mean	mean
All Alert Antibiotics	–0.704	–1.790	0.383	0.2	–0.266	–0.343	–0.189	<0.0001	4.031	1.598
Amphotericin (iv)	0.288	–0.343	0.918	0.4	–0.076	–0.123	–0.029	0.002	0.665	0.197
Cefotaxime	–0.036	–0.07	0.002	0.06	–0.001	–0.003	0.002	0.6	0.045	0.023
Ceftriaxone	0.058	–0.241	0.358	0.7	0.027	0.005	0.048	0.02	–0.391	–0.350
Ceftazidime	–0.518	–0.775	–0.262	<0.001	0.004	–0.015	0.023	0.7	0.468	0.286
Ciprofloxacin (iv)	0.063	–0.220	0.347	0.7	–0.030	–0.050	–0.010	<0.01	0.318	0.312
Meropenem	0.068	–0.285	0.420	0.7	–0.021	–0.047	0.004	0.1	0.197	–0.009
Piperacillin–tazobactam	0.281	–0.064	0.626	0.1	–0.086	–0.111	–0.061	<0.0001	0.796	0.321
Teicoplanin	–0.594	–1.031	–0.157	<0.01	–0.034	–0.065	–0.002	0.04	1.016	0.915
Vancomycin (iv)	–0.178	–0.437	0.080	0.2	–0.048	–0.067	–0.030	<0.0001	0.780	0.636

The maximum reduction in use was calculated from the difference between the observed values and the expected values, estimated by extrapolation of the pre-intervention line. The conservative reduction in use was calculated from the difference between the mean of observed values after the intervention and the intercept of the pre-intervention line in month 24, the last month before the intervention began. Data are presented in DDD/100 bed-days. LCI and UCI are the lower and upper limits of 95% confidence interval.

Table 3.2: Change in cost of Alert Antibiotics after the intervention

	Change in level				Change in slope				Maximum estimation of reduction	Conservative estimation of reduction
Antibiotic	mean	LCI	UCI	*P* value	mean	LCI	UCI	*P* value	mean	mean
All Alert Antibiotics	–730	–10020	8559	0.9	–1908	–2578	–1238	<0.0001	23852	9590
Amphotericin (iv)	2541	–3120	8202	0.4	–646	–1054	–238	0003	8075	1533
Cefotaxime	–50	–145	45	0.3	3	–4	10	0.4	–35	24
Ceftriaxone	233	–740	1206	0.6	85	15	156	0.02	–1067	–1108
Ceftazidime	–1504	–2160	–848	<0.001	10	–37	57	0.7	–123	826
Ciprofloxacin (iv)	451	–1554	2456	0.7	–206	–351	–61	0.006	2575	2092
Meropenem	572	–2485	3629	0.7	–230	–451	–10	0.04	2880	181
Piperacillin–tazobactam	1703	–330	3737	0.1	–544	–691	–397	<0.0001	6800	2035
Teicoplanin	–4251	–7316	–1187	0.008	–245	–475	–33	0.03	3173	3256
Vancomycin (iv)	–426	–1233	381	0.3	–126	–184	–68	<0.0001	1575	752

The maximum reduction in cost was calculated from the difference between the observed values and the expected values, estimated by extrapolation of the pre-intervention line. The conservative reduction in cost was calculated from the difference between the observed values after the intervention and the intercept of the pre-intervention line in month 24, the last month before the intervention began. LCI and UCI are the lower and upper limits of 95% confidence interval.

3.5.1 Costs of the intervention

The cost of the first year of the intervention, which included setting up the programs for extraction, formatting and analysis, was £15,143 and the cost of running the intervention in the second year was £4,990 (Table 3.3). The total cost of the intervention (£20,133) over the 2 years was therefore well below the most conservative estimate of the reduction in cost of Alert Antibiotics, which was £133,296 (the lower boundary of the 95% CI for change in slope after the intervention, £5,554 per month times 24 months). However, assuming that the cost of Alert Antibiotics would have continued to increase without the intervention, the cost of Alert Antibiotics was estimated to have decreased by an average of £23,852 per month (95% Cl £18,154- £29,549, P <0.0001) (maximum estimate of reduction, Table 3.2).

Table 3.3: Cost of the Alert Antibiotic Monitoring intervention and of the set-up and analysis of the ward antimicrobial supply database.

		2000–2001		2001–2002	
Activity	Resource	unit cost	per year	unit cost	per year
Data collection					
patient record form	photocopying	£0.03 per record	£14.76	£0.03 per record	9.06
identification of patients and completion of record form	ward pharmacist, 15 min per patient	£14.69 per h	£1806.87	£15.24 per h	1150.62
co-ordination of intervention	senior ID pharmacist, 1 h per month	£17.86 per h	£214.32	£18.53 per h	£222.36
data entry	clerical time	£0.05 per record	£24.60	£0.05 per record	£15.10
Data analysis					
set-up of database, data cleaning and programming for interrupted time series analysis	statistician, 6 months	£1606.58 per month	£9639.48	No cost year 2	
analysis and report writing	statistician, 5 days	£419.11 per week	£419.11	£434.61 per week	£434.61
supervision	consultant, 6 h per month	£216.00 per month	£2592.00	£225.60 per month	£2707.20
antibiotic policy committee	two meetings	£288.00	£432.00	£300.80	£451.20
Total costs			£15 143.14		£4990.15

3.6 Discussion

The study evaluated the intervention with one of the strongest quasi-experimental methods to evaluate the intervention. A systematic review showed fundamental methodological flaws in 70% of published evaluations of interventions to improve hospital antibiotic prescribing, especially in interventions defined as interrupted time series in methodology.[148] On the other hand, the cost- effectiveness analysis of the intervention that was performed in this study was a gap in previous studies. In the same review Davey et al, [148] found reliable data about financial outcomes were provided by 22 (34%) of the 64 studies, but only seven (11%) provided details about the intervention cost. The lack of cost of intervention was also mentioned in two other reviews. [234, 235] Furthermore, in this study average drug prices were used to avoid over-estimation as a result of possible price reduction of newly introduced drugs during the 4-year period.

The segmented regression analysis of a 4-year Interrupted Time Series showed that the Alert Antibiotics Monitoring Policy was associated with significant decreases in total use and cost in the 2 years after the Policy was introduced and implemented by clinical pharmacists. Even the most conservative estimate suggested that the cost of the intervention was more than offset by savings in drug costs by the second year of the intervention. Nonetheless, despite the success of the overall intervention, use and costs of Ceftriaxone increased. The intervention needed to expand to cover all antibiotics in order to assess the degree to which reduced use of Alert Antibiotics is associated with an increase use of other drugs.[229] Even if this does occur, the intervention, if continued, may remain cost-effective as the Alert Antibiotics are the most expensive anti-infectives. Therefore, this study provides evidence of a good financial case for targeting the inappropriate use of these drugs.

The Alert antibiotic intervention was successfully delivered by clinical pharmacists.

Measurement of hospital antibiotic use is a good start but needs to be supported by more detailed analysis of indications for use and outcomes. At present, collection of this information is laborious, requiring extraction from handwritten case records. The move towards electronic patient records is welcome but will not solve all of the problems inherent in the evaluation of antibiotic prescribing. Quality indicators require consensus about evidence-based clinical standards and about the information that must be recorded in order to evaluate compliance with standards.[220] Audits from Ninewells Hospital showed that <50% of prescriptions for antibiotics were supported by any information for indication of antibiotic treatment. [222] These results are depressingly similar to an audit from the Central Middlesex Hospital over 20 years ago.[139, 140] Electronic medical records will be easier to analyse than paper records, but the value of the information will be questionable unless the records include standardised, evidence-based minimum datasets for recording the indications for and outcomes of antimicrobial treatment.

3.7 Conclusion

The results showed that pharmacy stock data can be successfully and relatively easily used to assess the effect of interventions targeting antibiotics in hospitals. Adjustment of data by defined daily dose and for bed occupancy provide simple and objective measures of prescribing. The study is supported by a strong method for the evaluation of the intervention, quasi-experimental design to evaluate the overall impact of interventions to change prescribing.[206] The methods addressed the fundamental methodological flows in evaluation of interventions in 70% of published studies to improve hospital antibiotic use[236]. The Cochrane review by Davey et at. has evaluated the effectiveness and potential benefits of a range of interventions to improve antibiotic prescribing practices for hospital inpatients and emphasised on interrupted time series analysis as a robust method for evolution of interventions.[148] The Cochrane review

identified that reliable data about financial outcomes were provided in 22 (34%, 22 out of 64 studies) of the 64 studies, but only seven (11%) provided details about the intervention cost.[148] The lack of a control group could be seen as a limitation however, the change in Alert antibiotics use and cost (Figures 3.2 and 3.4) after the introduction of the intervention is so dramatic that we can be confident the effect is due to intervention.

Clearly these data do not provide information about the indication of treatment or clinical outcomes. However, clinical pharmacists or other staff can use ward supply data as a method of identifying wards with unusual usage pattern that could be targeted with more detailed audits. In Ninewells Hospital, these data provided important support for the continuation of the Alert Antibiotic intervention and for targeting interventions to improve the quality of antibiotic prescribing.[222, 237, 238] Having established the intervention and demonstrated its cost-effectiveness, the intervention team was put in a stronger position to request additional resources to analyse time trends in microbiology results and indicators of clinical outcome, such as length of stay and readmissions.[25, 238-240]

As in this study, clinical and hospital pharmacists have a crucial role in surveillance, management and interventions to improve patient care. Their contribution has been imperative for hospitals to convey prescribing education, reduce length of stay and economic saving. [148, 241-248]

The results of this study provided evidence that this investment was likely to result in net savings by the end of the 3-year period. The intervention team urged other UK hospitals to consider collection and analysis of these data. The data were available;

assurances could be given that the techniques required were not difficult and the methods could be shared with others.

CHAPTER FOUR: EUROPEAN SURVEILLANCE OF ANTIBIOTIC CONSUMPTION (ESAC) PROJECT

4.1 Introduction

In this chapter an overview of three phases of the ESAC project phases are provided: firstly, ESAC-1 for which the need for the ESAC-2 HC project was identified; secondly ESAC-2's aims, objectives and structure; and thirdly, the impact of ESAC-2 HC on establishing ESAC-3 HC.

The Hospital Care (HC) subproject of ESAC-2 consisted of three components namely longitudinal analysis of hospital antibacterial use, a point prevalence survey of antibacterials, and hospital characteristics. All three components are foundations for chapters 5, 7 and 8 of this thesis. Chapter 6 of this thesis is an additional survey in continuation of longitudinal survey of total antibacterial use.

Within ESAC-2 HC, I contributed to leading the project by writing the project protocol, recruiting hospitals and designing project components, in addition to undertaking data collection, processing and statistical analysis and project management and monitoring the scientific side of the project presented in this thesis.

4.2 ESAC-1 Project

Following the Copenhagen Recommendations[44] and acting on the Council of the European Union Recommendations of 15 November 2001 on the Prudent Use of Antimicrobial Agents in Human Medicine,[99] the ESAC project (European Surveillance of Antibiotic Consumption) was officially launched during the European Conference on Antibiotic Use in Europe organised on behalf of the Belgian EU Presidency in Brussels from 15-17 November 2001. The long-term objective was to promote "Good Antibiotic

Practice" and to contribute to a reduction of antimicrobial resistance in Europe. ESAC was led by Professor Herman Goossens at the University of Antwerp in Belgium.

A pilot project was established from 2001 to 2003 (referred to as ESAC-1) which was funded by the European Commission (Directorate-General SANCO – Health Monitoring Program). The goals of ESAC-1 was to document variations in antibiotic consumption and translate them into quality indicators for Public Health monitoring over time and place in order to target interventions and to assess the effectiveness of prevention programmes. During ESAC-1 actions were taken to harmonise the registration of antibiotic consumption in all EU Member States, in countries signatory to the European Economic Area as well as the applicant countries of Central and Eastern Europe. The ESAC-1 project aimed to develop a data collection system allowing production of comprehensive national data on the volume of antibiotic consumption, in ambulatory and in hospital care. Standardised national data were assembled in a European database for regional comparison of antibiotic use. [249]

Databases, which were available in certain countries using different systems for drug classification and for measurement of antimicrobial consumption, were further developed in a standardised, uniform and meaningful manner. Data collection was aggregated to the level of the active substance (not at brand level), using the taxonomy of the Anatomical Therapeutic Chemical (ATC) classification system, as recommended by the World Health Organisation (WHO). Consumption was expressed in defined daily doses (DDD).

Within the project the implementation of a standardised system for the exchange of antimicrobial consumption data between countries was necessary. Therefore a "network of networks" was created between the different Member States of the European

Community, countries signatories to the Agreement on the European Economic Area and associated countries of Central and Eastern Europe in order to facilitate communication and collaboration. This network approach allowed future communication and collaboration between all countries and could be broadened if other health related topics are found to be suitable for analysis in the same cross-nations way.[249]

ESAC had connections to other relevant networks like the European Antimicrobial Resistance Surveillance System (EARSS). It had further created national networks, compiled registers of available antibiotics, developed health indicators of antibiotic use with validation via linkages to resistance patterns in EARSS, detected seasonal and regional variations in consumption, consolidated the collection of antibiotic consumption, disseminated the knowledge in this field through a website and trained public health workers in differing European countries on standardised procedures. [250]

Within ESAC-1, the data on antibiotic use in European hospitals were from a selection of countries.[251] This was the first study at European level, but the hospital data in ESAC-1 had important limitations. Firstly, the estimation of national aggregates of hospital drug consumption should have been more critically evaluated. Some countries derive a reliable estimate for national hospital exposure to antibiotics from wholesalers' data; others from detailed consumption registration in all hospitals. In other countries, national consumption data are derived from a sample of hospitals, expressed in DDD per 100 bed days. Secondly, there is the problem of the denominator in expressing hospital consumption. In this cross-national comparison, ESAC were forced to express the aggregated national antibiotic consumption data as a function of the population of the country (DDD/1000 inhabitants per day) and not as a function of the number of bed days in the country (DDD/100 bed days), as recommended by the WHO and as had

been done in previous published analyses of hospital drug consumption. The healthcare data collection systems in Europe are not able to provide trustworthy, timely and comparable national data on the number of hospital bed days for all European countries. For those countries the source of available data differed in being either wholesale data or data provided by health care systems. Additionally, because the most recommended clinical activity denominator data, bed-days, were not available, the data were presented as DDD/inhabitants for hospital antibiotic use.[251, 252]

4.3 ESAC-2 project

In 2004 the European Commission Directorate-General SANCO – Health Monitoring Program (DG SANCO) supported a second phase of the ESAC project to run till 2007. The aim of the ESAC-2 project was to deepen the knowledge of antibiotic consumption in four specific areas: ambulatory care, hospital care, nursing homes and socioeconomic determinants of use.

The main objectives of ESAC-2 were:

To consolidate the continuous collection of comprehensive antibiotic consumption data in all European countries, for ambulatory care and hospitals,

- To disseminate its knowledge in the field of antibiotic consumption by the development of an interactive ESAC website,
- To develop health indicators of antibiotic use based on consumption data, to validate these indicators and to use a set of core indicators to give feedback on antibiotic consumption in the participating countries,
- To extend knowledge of antibiotic consumption, collecting additional data on a pilot basis,

- For ambulatory care, to link data on antibiotic use to patients' sex and age, prescriber and indication,
- For nursing homes, to collect data for individual nursing homes and to assess the assignment of these data to either ambulatory care data or hospital care data,
- For hospital care, to collect data for individual hospitals to link antibiotic use data to the hospitals' characteristics;
- Additionally to perform a pharmacoeconomic evaluation, including an assessment of determinants of use and regional variation. [253, 254]

4.3.1 ESAC-2 Hospital Care (HC) Subproject

The ESAC-2 Hospital Care (HC) subproject focused on consistent data collection from individual hospitals in order to develop a standard method that could be rolled out to other hospitals in the participating countries. The study aimed to explore:

- Trends in hospital antibiotic use over the study period;
- Effect of using different denominators (bed days or admissions) on longitudinal analysis of hospital antibiotic use;
- Relationship between the DDD calculated from total antibiotic use and the actual daily doses prescribed in each hospital.

The project had two principal components. First a Longitudinal Study (LS) with monthly data over a 6 year period and second a web based Point Prevalence Survey (PPS) using the Swedish PPS web-based tool the STRAMA (Swedish Strategic Programme for Rational Use of Antimicrobial Agents and Surveillance of Resistance). Another component, Hospital Characteristics was added later to explore the differences in hospitals and how they can affect different aspects of antibacterial treatment. The

preliminary target for the project was to recruit up to 15 hospitals so that the project could focus on ensuring that this was the first international project where data would be validated, processed and analysed, in order to provide a quality foundation for the future. However, 22 hospitals were eventually recruited, including one each in: Austria, Belgium, Croatia, Czech, Republic, Denmark, Estonia, Finland, France, Greece, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Slovenia, Sweden, Turkey and the four countries of the UK (England, Northern Ireland, Scotland and Wales). Clinical and hospital pharmacists were the leading clinical group in delivering the project (12 out of 22 or 55% hospitals).

Participation of the hospitals in project components was:

- PPS and LS & Questionnaire: 14 hospitals;
- PPS and LS: 2 hospitals;
- PPS and one year (2005) longitudinal data and Questionnaire: 2 hospitals;
- LS and Questionnaire: 2 hospitals; and
- PPS and Questionnaire: 2 hospitals.

For data privacy, each of the hospitals was assigned a number which is coherent in all the study components and publications and in this thesis. The original project protocol, written by me supported by feedback form the core group, is provided in Appendix A.4. Any updates and changes to the original protocol are described in the methods section in each of the ESAC related chapters. Findings from the ESAC-2 HC have been presented world-wide by me and the management team of the project either in international conferences or in formal ESAC meetings and other project related meetings.

4.4 ESAC-3 Project

In June 2007 the ESAC proposal for phase 3 was successfully accepted by the European Centre for Disease Prevention and Control (ECDC) for 2007-2010. ESAC-3 maintained a continuous, comprehensive and comparable (using ATC/DDD classification) database on antimicrobial consumption for all Member States, candidate countries and EFTA- EEA countries, ensuring high standards of data collection, collation and validation (using national registers) in a timely fashion. The project was designed to improve and expand the scope of the database developed in the ESAC project on consumption data on antiviral, antimycotic and anti-TB drugs in consultation with the ECDC.

The scope of ESAC-3 HC subproject was in-depth hospital care data collection. The objectives were to:

- Adjust ESAC-2 PPS for routine use;
- Organise a European-wide point-prevalence survey;
- Cluster the hospital antimicrobial consumption in an LS study according to the characteristics of the institutions and to the regional neighbourhood based on the method that was used in ESAC-2;
- Develop quality indicators of antimicrobial consumption in the hospital care sector.

For ESAC-3 HC, Professor Peter Davey was the ESAC Advisory Board and UK Network Leader and Dr Faranak Ansari was the ESAC Management Team member and leader of the HC subproject and Hospital Clinical Scientist until September 2008.[255-257] During this time, I wrote, set up and designed the project protocol in five components:

web-based PPS, LS, in depth analysis of ESAC-2, LS of antimicrobial use and resistance (EARSS data), hospital characteristics for more than 50 hospitals in 32 EU countries. I described the project components in ESAC-3 training workshops. I contributed to hospital recruitment across the Europe through ESAC-2 network and ESAC national representatives for additional countries. I assisted to hospital ground questions during the first PPS of the ESAC-3.

CHAPTER FIVE: ESAC LONGITUDINAL SURVEY 1: ANALYSIS OF TOTAL ANTIBIOTIC USE IN HOSPITALS FROM 18 EUROPEAN COUNTRIES

5.1 Background: The dilemma of the use of numerators and denominators in longitudinal surveys

Within the ESAC I project it was recognised that there is currently no unified hospital information on antibiotic use across the European countries.[251, 252] The explanations include lack of standardised methods for producing valid data either for hospital antibiotic use or for denominator data related to clinical activity[251, 252], such as occupied bed days or admissions. This chapter describes the work carried out by me. In my role as the co-lead for the ESAC-2 Hospital Care Project, I designed the study, recruited the hospitals and contributed to training workshops for participants. In my role as the researcher, I collected , processed the data and performed the statistical analysis. A study from the Netherlands suggested that an apparent increase in total antibiotic use from 1997 to 2001 was eliminated when the denominator was admissions rather than bed days. [189] The explanation was that there had been an increasing number of admissions over the period with decreasing mean length of stay.

5.2 Introduction

ESAC (European Surveillance of Antimicrobial Consumption) was established in 2000. In the first phase of the ESAC project data collection was limited to national sources of information about antibacterial use. Data about antibacterial use in ambulatory care were available from 26 countries[258] whereas only 15 countries could provide data about hospital antibacterial use.[259] Moreover the data did not include reliable information

about the number of occupied bed days (OBD) or admissions for the hospitals so the results were expressed as Defined Daily Doses (DDD) per 1,000 inhabitants. This is a reasonable measure of antibacterial use at the regional level but does not provide useful information for comparison of hospitals [259]. In the second phase of the ESAC project from 2004 to 2007 a hospital subproject was established to collect more detailed information from individual hospitals through longitudinal analysis of antibacterial consumption and point prevalence survey. The results of the first European point prevalence survey have been published.[260]

Reports on hospital antibiotic use have lacked detail about definitions of the units of measurement, which makes it difficult to compare results between hospitals or countries.[261] Longitudinal studies with well defined units of measurement have been published from multiple hospitals within the Netherlands[262] and Germany.[191] Both of these studies compared adjustment of antibiotic use for clinical activity with admissions versus occupied bed days and reported that total systemic antibacterial use increased when measured as DDD per 100 patient days, whereas it remained constant when expressed in DDD per 100 admissions. A possible explanation is that these hospitals had increasing numbers of admissions with shorter length of stay (LOS) over time.[191, 261, 262] However, it is not clear whether these results can be generalised to other countries. The aim of the ESAC longitudinal survey was to develop and test standardised methods for collection and statistical analysis of longitudinal data about hospital antibacterial use from different countries.

5.3 Aims

- What is the change in hospital antibiotic use over the study period?

- What effect do different denominators (bed days or admissions) have on longitudinal analysis of hospital antibiotic use?

5.4 Methods

ESAC national representatives were invited to participate in the study and recruit one hospital for the longitudinal survey. One hospital was selected from each of the following 18 countries: Austria, Belgium, Croatia, Czech Republic, Denmark, England, Estonia, Finland, France, Greece, Latvia, Netherlands, Norway, Scotland, Slovenia, Sweden, Turkey and Wales. With the exception of Turkey and Wales, the same hospitals also participated in the ESAC point prevalence study in June 2006.[260] Participants were asked to send data samples and to attend a workshop for discussion of the pilot data samples and for agreement on uniform databases was organised in January 2006. Data were submitted during February to June 2006. Hospitals were asked to provide monthly data for 6 years starting from January 2000 until December 2005: 15 hospitals provided six years data; one hospital provided five years data and two hospitals provided four years data. According to the project protocol total antibacterial dispensed were collected only to inpatient destinations, and clinical activity (occupied-bed-days or patient- day, and admissions) data for all inpatient destinations. Hospitals were not requested to separate their data by clinical groups and specialties because it was not possible for many participants and these data were not required to answer the study question.

The study only used aggregated data about consumption of antibiotics from hospital pharmacies and did not require approval from a Research Ethics Committee.

5.4.1 Measurement of drug use

The study focused on systemic antibacterials in the J01 sub-class according to ATC classification by the WHO Collaborating Centre for Drug Statistics plus, oral Metronidazole, Rifampicin, oral Vancomycin and Colistin [263, 264] Before submission of the main data, hospitals were asked to send a sample of their pharmacy stock data. Based on the samples, a simple Excel work sheet was proposed to the Study Group and discussed and agreed during the Prague workshop in January 2006. Minimum database requirements were:

- English drug names
- With their own ATC/DDD assignments
- Internal codes as an identifier for each product
- Strength, dosage form, and package content for each product in grams or international units
- Dispensing data for each antibacterial at product (code) level and on a monthly basis.

5.4.2 Clinical Activity Data

Participants also sent their monthly data on bed-days or patient-days and admissions together with the local definitions and methods of counting for each of these clinical activity variables. The criteria for clinical activity data, as well as pharmacy stock data, were the exclusion of outpatient clinics, day cases - both in bed-days and admission data - and transfers between wards and clinical groups from admissions. Since, in some countries, the administrative data on admission is, in fact, the sum of admissions to clinical groups and not to the hospital as one unit and, therefore, this could cause over

estimation of admissions to the hospital as a whole and under estimation of use if presented in DDD/admissions.

Confidentiality in data was essential for some hospitals and so, additionally, the project aim was to present the results in a blinded form without trying to compare hospitals by name or country. A number was assigned to each hospital which was coherent with the other components of ESAC-2 Hospital Care Project presented in chapter 6, 7 and 8 of this thesis, and in the reports, presentations and publications form ESAC-2 project.

5.4.3 Data validation and analysis

The total content per grams or unit of measurement was calculated for each product in all pharmacy stock databases. They were also assigned ATC codes and DDD content and when necessary corrections were made. The latest version of the ATC/DDD [265, 266] was used. Data processing was then applied to all 6-year data and were then put in a similar format to be analysed using Microsoft Access. An Access tool was designed to be used for analysing all databases. The following information was calculated automatically by the Access tool:

- Total use of antibacterials on a monthly, quarterly, and yearly basis given in DDDs, DDD/ 100 bed-days and in DDD/100 admissions.
- The same information for antibacterials included in the study subgroups at ATC level 4, and at substance level or ATC level 5.
- Similar information based on route of administration.
- Proportion of use for each substance according to route of administration.

For all variables from each hospital analysed, data were examined for homogeneity within time by examining the graphs and corresponding data.

Clinical activity data could not be validated. Team members obtained these data from a hospital's administration files and it would be time consuming and sometimes impossible for them to ask very detailed questions about the databases. Therefore, these data were provided by hospital administration files against a backdrop of different policies and different definitions in different hospitals within one country or countries.

5.4.4 Estimation of other clinical activity variables

A stock adjustment process used to estimate two additional clinical activity variables: number of discharges and length of hospital stay (LOS) from the data about admissions and OBD. A stock adjustment process is an accounting mechanism which shows how a certain stock accumulates over time given its net flow over time. In formula for the estimation of other clinical activity variables occupied bed-days denoted by B and number of in-patients admitted denoted by A, other clinical activity variables were obtained such as:

- Number of in-patients discharged, denoted by R, using the stock adjustment equation below where DPM is the number of days per month,

$$\frac{B_t}{DPM_t} = \frac{B_{t-1}}{DPM_{t-1}} + A_t - R_t ; \quad (5.1)$$

- Length of stay by an average in-patient, denoted by L, using the approximation

$$L_t = \frac{B_t}{\frac{A_t + R_t}{2}} \quad (5.2)$$

Professor Hassan Molana form Department of Economic Studies at the University of Dundee advised on the method for estimating other clinical activity variables.

For two hospitals the actual LOS for the study period were obtained to compare each of two datasets with estimated values. There was no statistically significant difference between actual and estimated values.

5.4.5 Statistical Analysis

Trends of use and clinical activity

In nearly all of the published studies, the only statistical analysis method that has been used is simple regression and this mainly on yearly data. Therefore, to acheive a better understanding of clinical and non-clinical users of the project with regard to the main research question, a simple regression analysis was first applied to all data including: DDD (defined daily dose), OBD (occupied bed-days or patient days), AD (admissions), LOS (length of hospital stay), DBD (DDD per bed-days or patient-days) and DAD (DDD per admissions). The level of antibacterial use and clinical activity variables differed widely across the hospitals. A method was needed to compare the change over time between similar variables and between different variables for each of the hospitals. Simple comparison of the slopes of regression lines was misleading. For example, a slope of 0.5 DBD/month (DBD is DDD/occupied bed-days) for a hospital with average or baseline use of 200 DBD is a change of 0.25% per month. In contrast,the same slope for a hospital with 50 DBD is a 1% change. Consequently, the slope of the regression line did not distinguish between a hospital with a higher level of baseline use but shallower slope *versus* a hospital with lower use but steeper slope. Therefore the result was the product of the intercept (baseline) values and the gradient of the slope (trend). In order to compare change in each variable over time, the slopes were scaled with their intercepts to produce the mean annual change using the following formula:

$$\% \Delta \text{ Variable} = [(\text{Slope} * 12)/ \text{Intercept}] * 100 \qquad (5.3)$$

For each hospital mean annual change was calculated with 95% Confidence Intervals (CI). Changes were considered significant if the 95% CI for the % difference did not cross zero.

Dynamic regression of time series

A better understanding of what determines the pattern of usage of antibiotics in hospitals is essential for a more effective monitoring of their impact, development of resistance, etc. To this end, DDD per bed-days or patient days or *YPB (Y use in DDD/ Bed-days)* constitutes the most commonly used measure analysed on the grounds that it represents the amount of antibiotic usage adjusted for 'clinical activity'. This is because *YPB* is believed to discount trends and/or fluctuations in the level of clinical activity and also to provide a comparable measure across hospitals. In fact a regression analysis can provide a more effective way of assessing whether such a scaling does take account of the level of clinical activity as well as allowing examination of the influence of other clinical activity indicators such as in-patient admissions, discharges and length of stay and the existence of exogenous trend and seasonality not captured by the latter explanatory variables. This involves estimating some version of the following general dynamic regression equation for each hospital:

$$Y_t = \sum_{s=0}^{S}\left(a_s Y_{t-1-s} + \beta_s A_{t-s} + \gamma_s B_{t-s} + \delta_s R_{t-s} + \phi_s L_{t-s}\right) + \sum_{j=0}^{J}\mu_j t^j + \sum_{i=2}^{12}\theta_i DM_{i,t} + \sum_{k=1}^{K}\lambda_k DI_{k,t} + \varepsilon_t \quad (5.4)$$

where *Y*, *A*, *B*, *R* and *L* are the variables explained above; $\alpha_s, \beta_s, \gamma_s, \delta_s$ and ϕ_s are the coefficients which capture the impact of these variables with *s* lags (assuming a finite lag order of $S \geq 0$); *t* refers to time associated with the observation date; the μ_j coefficients capture the intercept and trend (assuming some finite polynomial in time of degree $J \geq 0$); DM_i s are seasonal dummies which assumes 1 for month *i* and 0 otherwise

and whose coefficients, θ_i s, capture the shift in month with *i* relative to the first month (January is set as the bench month and dummies are used for February to December – *i*=2,...,12); DI_k s are dummies which capture irregularities such as sudden shifts in the series or outlier observations and assumes 1 for the relevant dates and 0 otherwise, hence the λ_k coefficients capture the corresponding shifts thus dampening their impact; and ε is a random disturbance term which, in general, can be allowed to follow an ARMA process. It is worth noting that a time series model of type

$$\Delta Y_t = \sum_{s=1}^{S} \alpha_s \Delta Y_{t-s} + \sum_{j=0}^{J} \mu_j t^j + \sum_{i=2}^{12} \theta_i DM_{i,t} + \sum_{k=1}^{K} \lambda_k DI_{k,t} + \varepsilon_t \,, \qquad (5.5)$$

where $\Delta Y_t = Y_t - Y_{t-1}$ is simply a special case of the regression equation in (5.4), *Y* is total use in DDD, *A* is admissions, *B* is bed-days or patient-days, *R* is discharge, and *L* is length of stay.

Y, *A*, *B*, *R* and *L* Statistical analysis was performed using EViews version 6 (QMS, Irvine, CA, USA). Professor Hassan Molana advised on regression modelling of time series and supervised using the EViews for the first analysis. However, due to changes in databases for a number of hospitals during re-validation of data and possible corrections for outliers the analysis had to be re-run and updated several times. The regression model, statistical analysis process and its techniques, relevant tests for selection of the best fitted model for each of the hospitals were performed as described in the Chapter 2 on times series and interrupted time series analysis.

5.4.6 Interpretation of Results

From a public health perspective the key question is “Is there evidence that the exposure of patients to antibiotics in this hospital may have increased or decreased over time?” The term “exposure of patients to antibiotics” encompasses any or all of these factors:

number of patients treated, unit doses administered or duration of treatment because they could all influence the measure of antibiotic use (DDD). The hospitals were separated into five groups based on the likelihood that change in exposure of patients to antibiotics had occurred:

Very likely: statistically significant changes in DDD that were not explained by changes in clinical activity.

Likely: statistically significant changes in DDD that were related to changes in clinical activity

Possible: no significant change in DDD but significant change in the same direction for DAD (DDD per 100/ Admissions) or DBD (DDD per 100 OBD)

Unlikely: change in the opposite direction for DDD and either DAD or DBD

Very unlikely: no significant change in DDD, DBD or DAD

5.5 Results

Eighteen hospitals participated in the longitudinal survey. Fifteen hospitals provided six years of data, one hospital provided five years of data and two hospitals provided four years of data. Two hospitals provided data for the year 2005 only and were therefore excluded from the longitudinal survey. All drug databases were built from pharmacy dispensing data.

Only a few hospital databases were patient-day in format with the definition of patient-day being: "duration of stay minus one day to count day of admissions and discharge as one day". In hospitals with bed-days data, the unit of measurement implied the number of occupied beds at a specific time, for example, at midnight 12:00 or at 8:00 in the

morning. One hospital, number 9, provided discharge data instead of admissions data. Participating hospitals confirmed that their data excluded transfers within the hospitals.

5.5.1 Hospital Characteristics

The 18 participating hospitals had a total of 13,664 beds (mean 759, range 242 to 2,459). Detailed information about case mix was returned from 16 hospitals with 12,411 beds, of which 12 were teaching hospitals with 11,164 beds (82% of the total) and seven were tertiary care hospitals with 7,572 beds (55% of the total). At least one Intensive Care Unit was present in each hospital; 12 had paediatric units and seven hospitals had a pediatrics ICU; 13 hospitals had haematology units, 11 had renal dialysis units and 10 had Infectious Diseases departments. Hospitals number 5 and 17 were infectious diseases hospitals. Sixteen hospitals also participated in the ESAC point prevalence survey[260] and were identified by the same numbers in both surveys.

5.5.2 Data Validity

During data validation and analysis the following problems captured in the databases:

- Extracting and sending data directly from pharmacy stock without a control or testing the validity of them,
- Product names, drug content and strength given in non English language,
- Databases with trade names only,
- Variations in the definition and understanding of the term " generic name" across the countries,
- Different database structures within the 6 year period from one hospital,
- Errors in ATC codes and DDDs,
- Mistakes by data providers in translating the trade name into a generic name - for a few products the real drug name could not be found in drug

dictionaries. The name found in Google just had to be trusted and used and was passed to hospital colleagues.

- More problematic trade names when the product was produced for use outside Europe and internet resources were difficult to find to search for the real drug name,
- Similar internal codes for different products or for products with different strengths,
- Different coding system across the whole 6-year period without rectifying or notifying this problem to the data analyst.

Pharmacy stock data validation became the most time consuming phase of the project. Around 3,800 products were checked one by one and ATC/DDD assigned to each product before data analysis. More discrepancies were found during and after data analysis. Active communication with data providers could resolve some of the inconsistencies in databases. Corrected parent product lists were sent back to hospitals.

5.5.3 Preliminary analysis

A preliminary time series showed two problems: first, one or more structural breaks and second, extreme outliers. Discrepancies were discussed with data providers. The data were cleaned to eliminate contamination or errors in data entry as much as possible. Nonetheless, some outliers and structural breaks could not be resolved.

To enable a better understanding, time plots for all data are provided in Tables A.5.1.1 to 7 in Appendix A.5.1. Tables A.5.1.8-10 in Appendix A.5.1 represent the plots of unadjusted use versus bed-days, admissions and length of stay.

It is useful to look at pattern followed by the variables *Y* (use), *B* (bed-days) and *A* (admissions), *L* (length of hospital stay), and *R*(discharge) for which data were provided by the hospitals in Tables A.5.1.1-5 (Appendix A.5.1). First, it is clear that there are great variations between the hospitals in either data or corresponding graphs. However, some hospitals have more similar time series. Disregarding the outliers, it is clear that in general these series contain a predictable component, and that the pattern followed for each variable varies across hospitals. For example, looking at plots of *Y*, we see that (i) in some hospitals fluctuates around a positive or negative trend while in others it simply changes around a constant mean and (ii) the extent of unpredictability of these fluctuations vary across hospitals. In addition to *Y*, *B* and *A*, it was observed that R and *L* (which were estimated) behave similarly with close values for most of the hospitals. As can be seen by comparing Tables A.5.1.3 and 5 (Appendix A.5.1), admissions and discharges follow a close pattern in all hospitals. Thus the difference between admissions and discharges seems to be a stationary mean zero random variable with a strong seasonal and autoregressive pattern. Table A.5.1.4 (Appendix A.5.1) illustrates how hospitals also exhibit differences with respect to the length of time they keep an average in-patient since *L* shows fluctuations around a negative trend in some of the hospitals whilst in others it oscillates around a constant mean.

5.5.4 Mean yearly change in antibacterial use

Mean monthly total use was 14,190 DDD and ranged from 2,791 DDD in hospital 12 to 53,195 DDD in hospital 17. Total antibacterial use measured in DDD increased in 14 of the 18 hospitals and decreased in four (Figure5.1, Table 5.1). The changes were statistically significant for eight hospitals with increasing use (hospitals 2, 6, 7, 11, 12, 14, 15 and 18) and for three hospitals with decreasing use (hospitals 1, 8 and 9, (Figure 5.1, Table 5.1)

5.5.5 Adjustment for clinical activity

Changes in clinical activity

The mean number of admissions was 2,928, range from 659 to 7,269 per month. Admissions increased in 10 hospitals and decreased in 8 hospitals. Changes were significant in 5 hospitals (Figure 5.2, Table5.2). Mean monthly OBD was 18,222, range from 6,435 to 49,567. OBD increased in 5 hospitals and decreased in 13 hospitals (Figure 5.2, Table5.2).

Comparing changes in admissions with OBD, only hospital 12 had a statistically significant increase in admissions and OBD. Of the remaining 9 hospitals with significant increases in admissions, five had no significant change in OBD (hospitals 2, 6, 8, 16, 18) and three had significant decreases in OBD (hospitals 4, 9, 11).

Mean LOS was 6.65 days, range from 3.0 days to 10.8 days. LOS decreased in 15 hospitals and the change was significant in 13 hospitals (Figure 5.2, Table5.2). Hospitals 3, 12 and 13 had small increases in length of stay that were not statistically significant (Figure 5.2, Table5.2). These changes in LOS probably explain most of the discrepancies between changes in admissions and OBD. The hospital with significant increase in both admissions and OBD (hospital 12) had a small, non significant increase in LOS (Figure 5.2, Table5.2). In contrast, LOS decreased in all of the 8 hospitals with increase in admissions but either no change or decrease in OBD.

Table 5.1: Mean annual percentage of change in DDD, DDD per bed-days (BD), DDD per admissions (DAD) for each hospital given with confidence intervals (CI) and P values.

Hospital Number	DDD, CI and P value	DBD, CI and P value	DAD, CI and P value
1	-2.95 (-4.66 , -1.41) >0.01	0.20 (-1.33 , 1.59) 0.8	-2.68 (-4.20 , -1.30) >0.01
2	9.87 (8.79 , 10.84) >0.01	9.84 (9.02 , 10.60) >0.01	8.62 (7.52 , 9.61) >0.01
3	2.02 (-0.31 , 4.00) 0.09	0.96 (-3.51 , 4.34) 0.6	0.87 (-2.89 , 3.82) 0.6
4	1.10 (-0.17 , 2.26) 0.09	2.69 (1.37 , 3.89) >0.01	-1.71 (-3.50 , -0.10) 0.04
5	3.86 (-11.09 , 10.62) 0.5	15.86 (6.33 , 19.67) 0.01	9.98 (-2.95 , 15.39) 0.09
6	6.17 (3.77 , 8.06) >0.01	5.31 (2.66 , 7.38) >0.01	3.64 (0.49, 6.03) 0.03
7	6.68 (4.78 , 8.30) >0.01	13.15 (11.57 , 14.47) >0.01	8.94 (7.05 , 10.52) >0.01
8	-3.44 (-6.41 , -0.93) >0.01	-3.46 (-6.62 , -0.83) >0.01	-4.59 (-7.65 , -2.01) >0.01
9	-4.96 (-7.16 , -3.03) >0.01	-3.16 (-5.14 , -1.41) >0.01	-6.58 (-8.91 , -4.55) >0.01
10	0.56 (-0.70 , 1.71) 0.4	1.62 (0.47 , 2.69) 0.007	1.20 (-0.11 , 2.39) 0.07
11	1.82 (0.62 , 2.92) >0.01	2.93 (1.83 , 3.95) >0.01	0.18 (-1.19 , 1.43) 0.8
12	3.58 (-0.09 , 6.42) 0.06	-10.57 (-16.26 , -6.16) >0.01	-10.26 (-15.73 , -5.60) >0.01
13	0.10 (-1.76 , 1.74) 0.9	0.55 (-1.256 , 2.15) 0.5	0.86 (-1.08 , 2.56) 0.4
14	4.21 (2.03 , 6.05) >0.01	4.91 (2.99 , 6.56) >0.01	2.40 (0.1, 4.35) 0.04
15	2.57 (0.82 , 4.12) 0.01	8.42 (6.70 , 9.88) >0.01	5.05 (3.08 , 6.73) >0.01
16	2.67 (-0.48 , 5.09) 0.1	3.87 (0.767 , 6.23) 0.02	-6.14 (-10.14, -2.99) >0.01
17	-1.80 (-5.77 , 1.35) 0.3	0.64 (-3.11 , 3.59) 0.7	-0.25 (-3.99 , 2.72) 0.9
18	1.26 (0.08 , 2.25) 0.04	0.38 (-0.90, 1.54) 0.5	-0.46 (-2.34, 1.21) 0.6

Table 5.2: Changes in clinical activity- Mean annual percentage of change in Bed-days (BD), and Admissions (AD), and Length of stay (LOS) for each hospital given with confidence intervals (CI) and P values.

Hospital Number	BD, CI and P-Value	AD, CI and P value	LOS, CI and P value
1	-3.08 (-4.25, -1.99) >0.01	-0.25 (-1.02 , 0.49) 0.5	-2.85 (-3.59 , -2.13) >0.01
2	0.13 (-0.66 , 0.89) 0.7	0.79 (-0.07 , 1.60) 0.07	-0.72 (-1.34 , -0.13) 0.01
3	0.64 (-2.45 , 3.17) 0.7	0.57 (-0.88 , 1.88) 0.4	0.39 (-2.96 , 3.09) 0.8
4	-1.43 (-2.20 , -0.71) >0.01	3.19 (2.14 , 4.15) >0.01	-3.88 (-4.45 , -3.32) >0.01
5	-6.11 (-7.10 , -5.17) >0.01	-3.92 (-4.96 , -2.94) >0.01	-2.81 (-3.49 , -2.15) >0.01
6	0.65 (-1.00 , 2.11) 0.4	1.99 (-0.13 , 3.77) 0.06	-1.36 (-2.43 , -0.38) >0.01
7	-3.31 (-4.30 , -2.38) >0.01	-1.28 (-2.23 , -0.39) >0.01	-2.10 (-2.67 , -1.56) >0.01
8	-0.06 (-0.67 , 0.52) 0.8	1.45 (0.69 , 2.17) >0.01	-1.47 (-2.22 , -0.75) >0.01
9	-2.36 (-4.67 , -0.38) 0.02	2.87 (-0.05 , 4.66) 0.05	-4.10 (-5.17 , -3.10) >0.01
10	-1.02 (-1.80 , -0.28) >0.01	-0.64 (-1.48 , 0.16) 0.1	-0.41 (-0.86 , 0.02) 0.06
11	-1.01(-1.58 , -0.45) >0.01	1.61(0.73 , 2.43) >0.01	-2.43 (-2.98 , -1.89) >0.01
12	26.28 (25.59 , 26.71) >0.01	24.67 (23.80 , 25.27) >0.01	1.43 (-3.37 , 4.97) 0.5
13	-0.38 (-0.91 , 0.13) 0.1	-0.61 (-1.43 , 0.17) 0.12	0.40 (-0.23 , 0.99) 0.2
14	-0.44 (-1.06 , 0.15) 0.1	-0.16 (0.83, 2.31) >0.01	-1.68 (-2.39, -1.01) >0.01
15	-4.30 (-6.11, -2.67) >0.01	-2.10 (-3.83 , -0.54) >0.01	-2.50 (-3.46 , -1.59) >0.01
16	-1.16 (-3.91 , 1.09) 0.3	19.35 (18.17 , 20.12) >0.01	-8.09 (-10.61 , -5.92) >0.01
17	-2.31 (-2.64 , -1.99) >0.01	-1.48 (-1.99 , -0.98) >0.01	-0.93 (-1.22 , -0.64) >0.01
18	0.92 (-0.46 , 2.17) 0.2	1.93 (0.28 , 3.40) 0.02	-0.96 (-2.41 , 0.36) 0.2

Figure 5.1: Hospitals ranked by mean percentage of change in total use, DDD

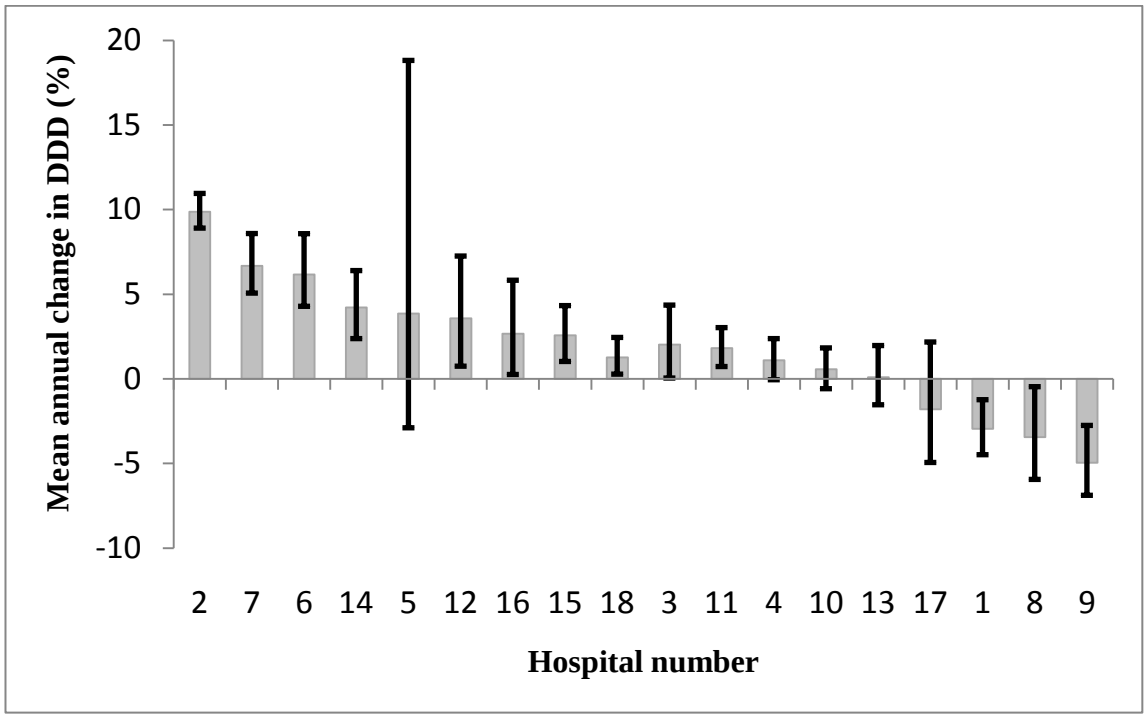
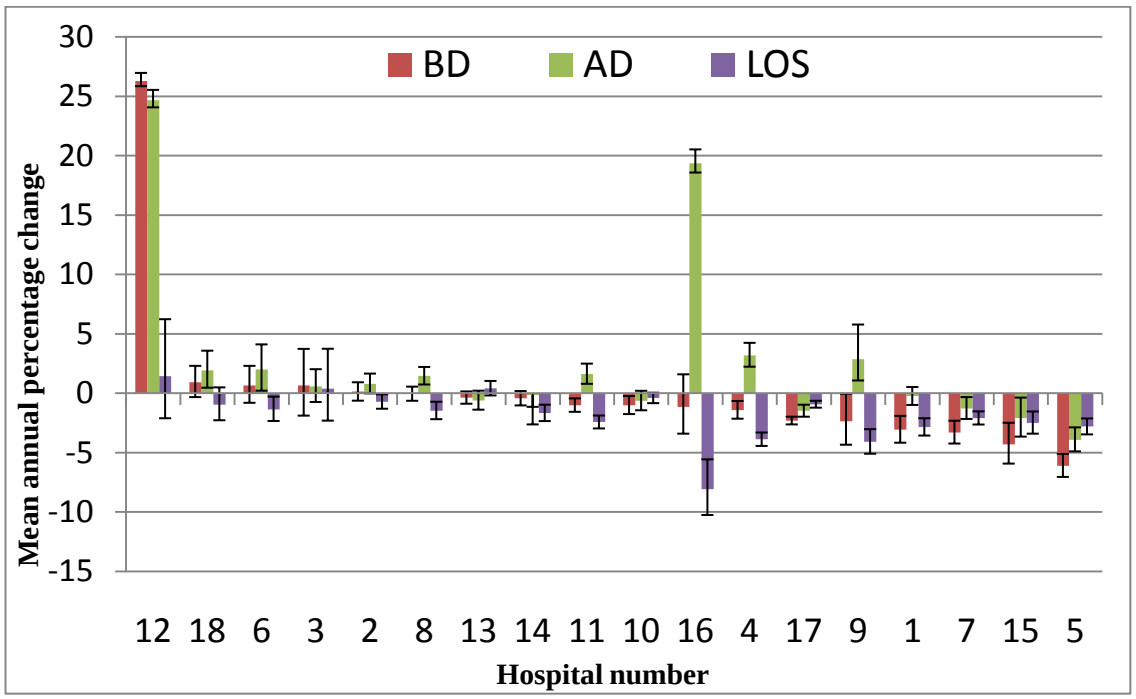


Figure 5.2: Mean annual percentage of change for Clinical activity variables ranked by changes in OBD (occupied bed-days), AD (admissions), LOS (length of stay)



Total antibacterial use adjusted for admissions and occupied bed days

There was considerable variation between hospitals in both measures of adjusted antibiotic use. Mean monthly use in DBD was 83.7, range 16.5 to 351, the ratio between highest and lowest hospital was 21.3. Mean monthly use in DAD was 505, range 171 to 1,499, the ratio between highest and lowest hospital was 8.8. With only two exceptions (hospitals 12 and 13) adjustment of DDD by OBD resulted in larger changes over time than adjustment by admissions (Table 5.1, Figure 5.3).

For most hospitals adjustment for either bed days or admissions made little difference to the scale or statistical significance of changes in DDD (Table 5.1, Figure 5.3). For hospitals 5 and 10 the changes were in the same direction with DDD, DBD and DAD but only statistically significant for DBD. However, in three hospitals changes in DDD, DBD and DAD were not in the same direction. Hospital 12 had significant change in the opposite direction to DDD for both DBD and DAD (Table 5.1, Figure 5.3). This hospital had a large (25%) increase in admissions with no significant change in length of stay, consequently adjustment of change in DDD for either admissions or OBD gave similar results, in this case a reversal of the trend in DDD because of the large increase in clinical activity measured with either admissions or OBD. For hospitals 4 and 16 there was a non-significant increase in DDD with statistically significant increase in DBD but statistically significant decrease in DAD (Table 5.1, Figure 5.3). These discrepancies probably occurred because both hospitals had statistically significant increases in admissions with statistically significant decreases in length of stay.

For a better understanding of changes in all variables, ranking hospitals by mean change in use and clinical activity variables is summarised in Figure 5.4.

Figure 5.3: Mean annual percentage of change for DDD, DBD (DDD/bed-days) and DAD (DDD/ admissions) ranked by changes in DDD

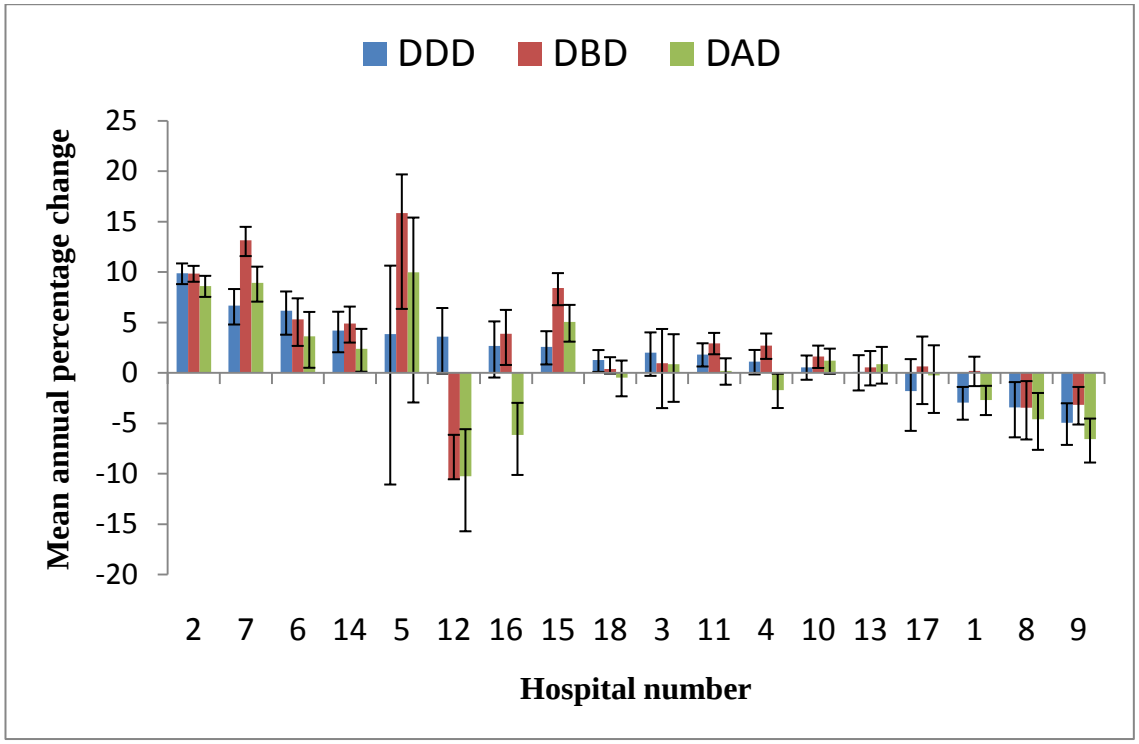
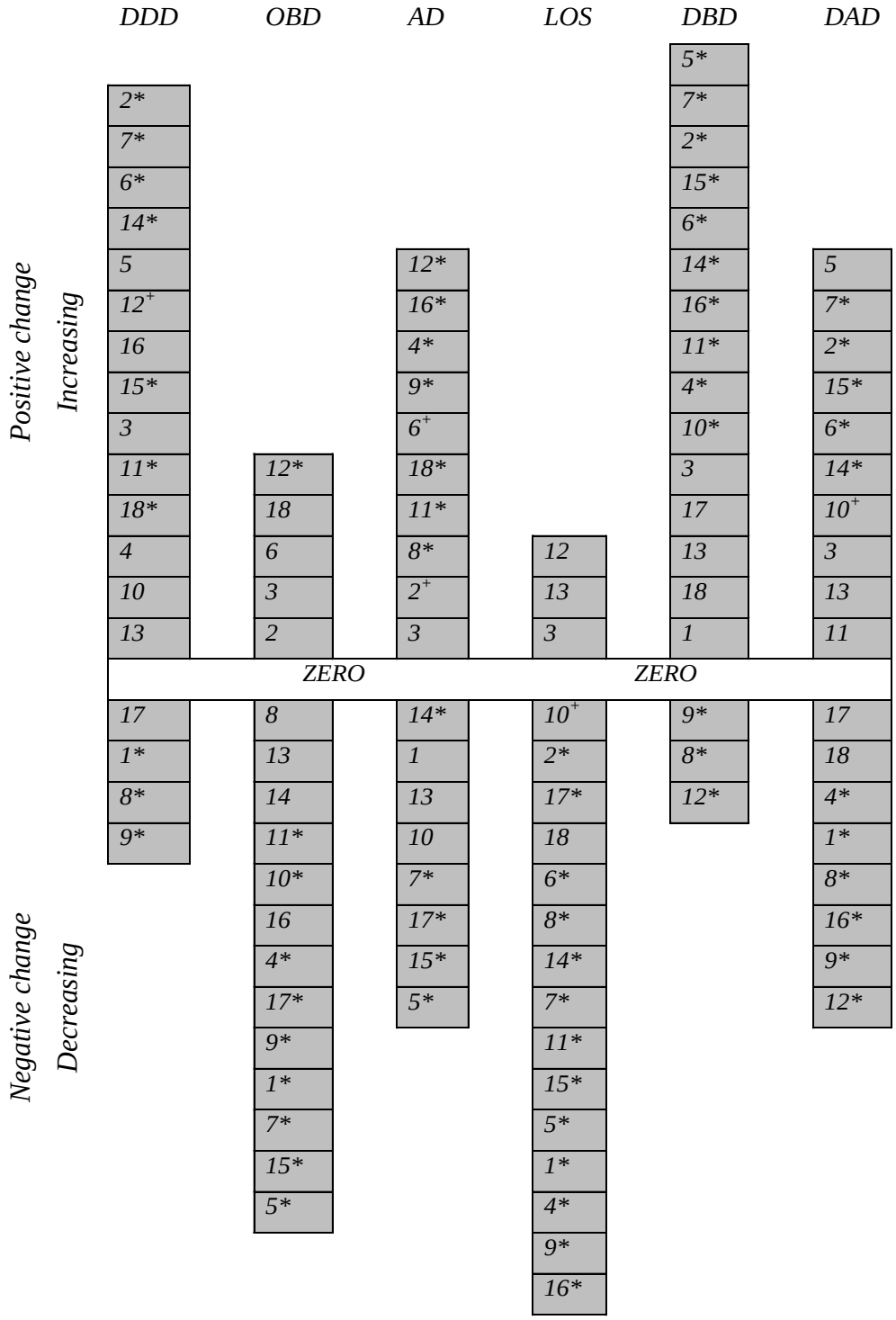


Figure 5.4: Ranking hospitals by mean change in use and clinical activity variables. Significant changes are marked with star. Changes with P values 0.06 or 0.07 are marked with positive. (DDD defined daily dose, OBD: occupied bed-days, LOS length of hospital stay, DBD: DDD/100 bed-days, DAD: DDD per 100



5.5.6 Time series analysis

The results of regression analysis of the time series for individual hospitals are given in this section. Complete output of the regression analysis for each hospital is provided in Appendix A.5.2. One of the regression models is provided in Figure 5.5 with explanation of the results. Given that one of the aims in doing so is to find the extent to which *B*, *A*, *R* and *L* explain *Y*, this was done preliminary by checking the plots of *Y* against each of *B*, *A*, and *L* which are given in Tables A.5.1.8 to 10 (Appendix A.5.1). Again, disregarding those cases in which the existence of outliers distort the picture (mainly hospitals 5, 9, 12, 14, and 17), it is clear that the extent of correlation between these variables and *Y* varies significantly across the hospitals. For instance, looking at Table A.5.1.8 (Appendix A.5.1), which shows plots of *Y* against *B*, we see that in hospitals 1, 2, 6, 9, 10, 14, 16, 17 and 18 exhibit some positive correlation while there is no evidence of any correlation for hospitals 3, 4, 7, 8, 12, and 13.

The regression analysis is carried out using either the model given in formulas 4 and 5 or the logarithmic version, to take account of the non-linearity in the underlying series as the starting point, and simplifies the estimated relationship to obtain a prudent empirical model which is statistically robust. The results are summarised in Table 3 and are provided in detail in Appendix A.5.2 and suggest that, in general, hospitals behave differently in their antibiotic usage and, in particular, the clinical activity variables do not always play a significant role.

It is found that in six of the hospitals (numbers 4, 7, 8, 13, 14, and 17) antibiotic use seems to behave autonomously, with no impact from the clinical activities being present; in hospitals 8 and 17 its behaviour has an autoregressive nature, in 7 and 14 it is driven by time trend, and in 4 and 13 the dynamics can be attributed to the disturbances.

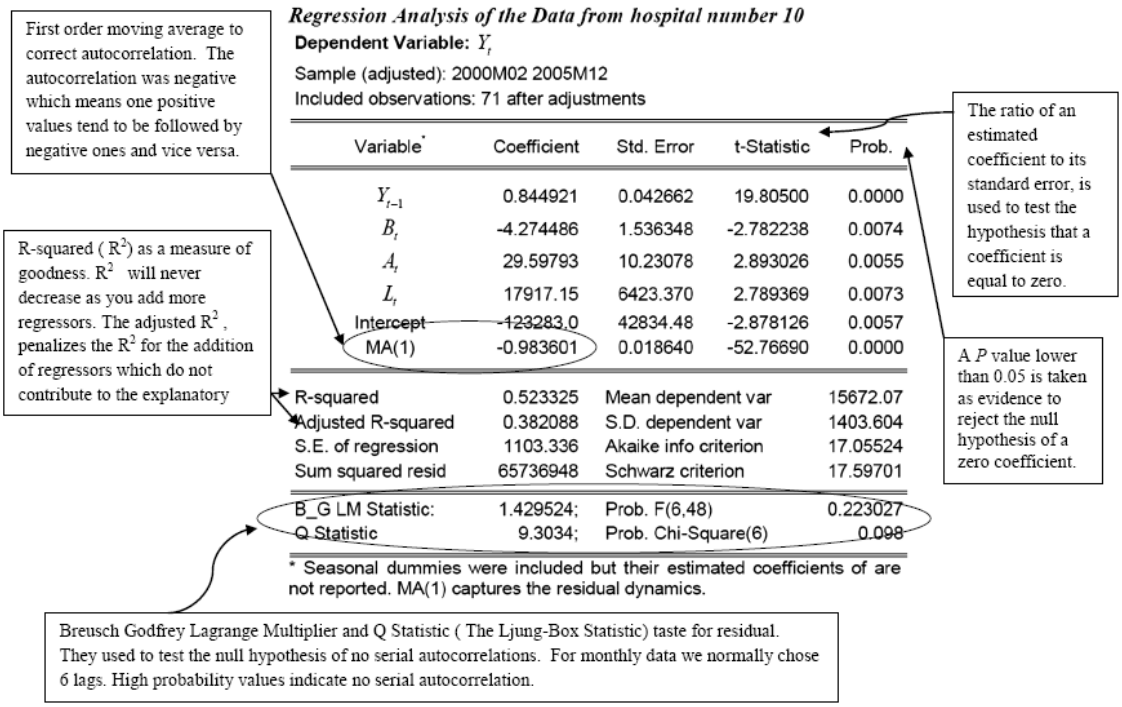
In three of the hospitals (numbers 11, 16, and 18) the clinical activity variables that influence antibiotic usage exclude the most commonly used factor, therefore, B or occupied bed-days does not feature directly as a significant explanatory factor. In hospital number 11, length of stay and discharge can explain the total use. In hospital 16, admissions is the only direct explanatory factor for total use and in hospital 18, all three other clinical activity variables play determining roles on total use.

In the remaining nine hospitals (numbers: 1, 2, 3, 5, 6, 9, 10, 12, and 15) occupied bed-days, admissions, discharges and length of stay feature in one way or another as significant explanatory variables. Only in three hospitals (number 1, 2, and 6) do occupied bed-days happen to be the only relevant clinical activity variable. In hospital number 3, length of stay is the only clinical activity variable without direct impact on total use. In hospitals 5 and 15, all clinical activity variables in the model can directly determine the total use.

Table 5.3: Regression analysis of time series for each hospital, summary of the best fitted model. Y: DDD, B: occupied bed-days, A: admissions, L: length of stay, R: discharge, AR: autoregressive order, MA: moving average order

Hospital	Regression equation model
1	$Y = 0.45\ B_t - 17$
2	$Y_t = 0.9\ B_t - 0.73t^2 + 5175$
3	$Y_t = 24800 - 8\ B_t + 8\ B_{t-1} + 242\ A_t - 245R + [MA(1)=0.34]$
4	$\Delta Y_t = 56 - 0.8\ \Delta Y_{t-1} - 0.49\ \Delta Y_{t-2}$
5	$\Delta \text{Ln}\ Y_t = 7.7\ \Delta \text{Ln}\ B_t - 342\ \Delta \text{Ln}\ A_t - 369\ \Delta \text{Ln}\ R_t - 710\ \Delta \text{Ln}\ L_t - 0.32\ \text{Ln}Y_{t-1} + 865\ \text{Ln}\ B_t - 417\ \text{Ln}\ A_{t-1} - 448\ \text{Ln}\ R_{t-1} - 866\ \text{Ln}\ L_{t-1} + 6$
6	$Y_t = 0.43\ B_t + 13_t - 1868 + [AR(1)= -0.39]$
7	$Y_t = 4041 - 14\ t + 0.46\ t^2$
8	$\text{Ln}\ Y_t = 0.002\ t + 9.7 + [AR(1)=0.40]$
9	$Y_t = 0.74\ B_{t-1} - 2.85\ A_{t-1} + 4354 + [MA(1)= 0.97] + [\ AR\ (1) = -0.60]$
10	$Y_t = 0.8\ Y_{t-1} - 4\ B_t + 30\ A_t + 17917\ L_t - 123283 + [MA(1)=-0.98]$
11	$\text{Ln}\ Y_t = 0.98\ \text{Ln}\ R_t + 1.17\ \text{Ln}\ L_t + 0.01\ t - 6.7E\text{-}05\ t^2 - 1.1$
12	$Y_t = 0.34\ Y_{t-1} - 0.09\ B_t + 1.6\ A_t + 169\ L_t - 519 - 13\ t$
13	$\Delta Y_t = 0.5 - 0.9\ \Delta Y_{t-1} + [MA(2)= -0.96]$
14	$\text{Ln}\ Y_t = 10 + 0.02\ t - 0.0002\ t^2$
15	$\Delta \text{Ln}\ Y_t = 500\ \Delta\ \text{Ln}\ B_t - 240\ \Delta \text{Ln}\ A_t - 263\ \Delta \text{Ln}\ R_t - 503\ \Delta \text{Ln}\ L_t - 0.1\ \text{Ln}Y_{t-1} + 483\ \text{Ln}\ B_{t-1} - 230\ \text{Ln}\ A_{t-1} - 254\ \text{Ln}\ R_{t-1} - 484\ \text{Ln}\ L_{t-1} + 0.01\ t + 12.4$
16	$Yt = 0.77\ A_t + 4131$
17	$Y_t = 42198 + [AR(1)=0.53]$
18	$Y_t = 3\ A_t + 1.3\ R_t - 3.6\ R_{t-1} + 2296\ L_t - 1130\ L_{t-1} + 30_t + 12989$

Figure 5.5: Interpretation of regression of time series results for one of the hospitals



5.6 Discussion

This is the first study to use a standardised method to collect data on antibacterial use from hospitals in different countries. Previous studies have focused on individual hospitals or on multiple hospitals from single countries. [191, 262, 267, 268] Collection of data from hospitals in 18 different countries has provided a wide range of antibiotic use and of changes in clinical activity over time. Measurement of drug use in DDD is the foundation of the WHO Collaborating Centre for Drug Statistics Methodology. It is especially important for international studies when drugs have different trade names and strengths in different countries. In the ESAC HC Subproject ATC/DDD was assigned by a central team. This required considerable time and effort because and it was found that many hospitals did not assign ATC/DDD correctly. Furthermore, in some hospitals

there were several trade names for one product, including a few that were manufactured for use in countries outside Europe. Further research is required to understand the importance of these errors and improve the reliability of alternative methods for data collection, such as web based methods for assisting hospitals with ATC classification and calculation of defined daily doses. Central processing of data is unlikely to be sustainable in all countries.

Use of antibacterials increased over time in 14 hospitals and decreased in four hospitals. The change was statistically significant in 11 hospitals (Figure5.1, Table5.1). However, there were marked changes in clinical activity with decreasing length of stay in 15 hospitals and increasing admissions in nine hospitals (Figure5.2, Table5.2). Analysis of changes in clinical activity is therefore critical for the final interpretation of results.

5.6.1 Changes in clinical activity

The WHO recommended method for surveillance of drug use in hospitals is to divide DDD by OBD.[269] However, OBD is itself a complex measure determined by the number of admissions, their LOS and the hospital's occupancy rate [270] Our results show the importance of a clear, stepwise approach to the interpretation of the data. Overall our results supported the hypothesis that DBD would show greater annual change than DAD due to an underlying reduction in length of stay. However, this trend was not universally present. Moreover there were four hospitals with extreme results that clearly demonstrated the potential complexity of changes in admissions and LOS that are not obvious from measurement of OBD alone (Figure 5.3, Table 5.2), hospitals 4, 9, 12 and 16). Our results support the recommendations to include both admissions and OBD in surveillance of antimicrobials[261] but it is proposed that interpretation is facilitated by calculation of LOS from admissions and OBD (Figure 5.3, Table5.2).

5.6.2 Interpretation of results

In addition to allowing multivariate adjustment for clinical activity the time series analysis accounted for outlier, extreme results and for structural breaks (step change) in the data. The combination of analysis of mean annual change with time series analysis allowed us to separate the hospitals into five groups based on likelihood of change in exposure of patients to antibiotics (Table 5.4). Further research is required to assess the clinical importance of these distinctions. In order to test the hypothesis that likelihood of change in exposure of patients to antibiotics is related to changes in antimicrobial resistance. ESAC is currently collecting data from a larger sample of hospitals that have participated in the European Antimicrobial Resistance Surveillance Scheme.[271] In addition to analysis of total antibiotic use the time series model will also be used to analyse changes in use of classes of drugs such as Quinolones or third generation Cephalosporins that have been previously linked with changes in antimicrobial resistance and *C difficile* infection.[272] The time series model proposed in this chapter will also facilitate the evaluation of interventions to change antibiotic use[148] by identifying step changes or progressive changes that cannot be explained by change in clinical activity.

Table 5.4: Overall interpretation of change in antibiotic exposure in the 18 hospitals from the results of statistical analysis of mean annual change and time series analysis of antibiotic use

Likelihood of change in antibiotic exposure	Change in DDD[1]	Hospitals	Mean change in antibiotic use	Time series analysis of antibiotic use
Very likely	Decrease	8	Statistically significant change in the same direction for DDD[1], DAD[2] and DBD[3]	Change in DDD[1] independent of clinical activity in all hospitals
	Increase	7, 14		
Likely	Decrease	1,9	Statistically significant change in the same direction for DDD[1] and either DAD[2] or DBD[3]	Change in DDD[1] related to change in clinical activity in all hospitals
	Increase	2, 6, 11, 15		
Possible	Decrease	No hospitals	No significant change in DDD[1]. Significant change in the same direction for DAD[2] or DBD[3]	Change in DDD[1] related to change in clinical activity for both hospitals 5 and 10
	Increase	5, 10		
Unlikely	Decrease	No hospitals	Opposite change in direction for DDD[1] and either DAD[2] or DBD[3]	Change in DDD[1] related to change in clinical activity in hospital 12, 16 and 18 but not in 4
	Increase	4, 12, 16, 18		
Very unlikely	Decrease	17	No significant change in DDD[1], DAD[2] or DBD[3]	Change in DDD[1] related to change in clinical activity in hospital 3 but not in 13 or 17.
	Increase	3, 13		

Abbreviations: DDD[1] defined daily doses; DAD[2] defined daily doses per 100 admissions; DBD[3] defined daily doses per 100 occupied bed days

5.6.3 Strengths and weaknesses

Strengths of this study are that standardised methods were used to collect and analyse longitudinal data from multiple countries with a wide range of antibiotic use and clinical activity. This study has addresses several of the weaknesses identified in previous studies by using a standardised method for conversion of drug use to DDD, clearly defined definitions of bed days and admissions and collection of monthly data.[261] In this study the effects of additional denominator of clinical activity were further explored. Furthermore, estimated were discharge and length of stay and used that in future studies can be replaced with actual data when available. A new method for statistical analysis of trends over time and for the regression of time series analysis of antibacterial use was established. Combination of analysis of mean change in antibiotic use per year with time series analysis enabled identification of hospitals in which exposure of patients to antibiotics probably has or has not changed over time. Having established the model for the impact of clinical activity variables on total use and identified differences in changes over time with using different denominator of clinical activity, further studies are suggested to describe more explanatory factors for changes in antibiotic use and differences in changes between the hospitals. For example, in future studies it would be helpful to have data about changes in antibiotic policy and case mix over time. Changes in antibiotic policy can affect the total use in DDD for example a shift in prescribing for intra-abdominal infection from a combination of amoxicillin plus Gentamicin plus Metronidazole, to monotherapy with Piperacillin-Tazobactam would reduce the associated DDDs by two-thirds. Information about hospital characteristics in the final year of data collection were collected but hospitals were unable to provide data about changes in case mix (e.g. proportion of paediatric beds) throughout the study period.

This study does have some potentially important weaknesses. It was impossible for a number of hospitals to exclude dispensing at discharge from their pharmacy supply data. However, none of the hospitals had changed their dispensing system over the study period so this should not have had a major influence on our longitudinal analysis. Nonetheless, LOS did reduce over the study period in most hospitals and therefore the number of patients with length of antibiotic treatment greater than length of stay is likely to be increasing. It would be helpful for future studies to document the impact of dispensing at discharge. Only 18 hospitals were included in total and that the period of the longitudinal survey did not include the year of the point prevalence survey[260] so there is no concurrent information about prescribed daily doses.. Having established the methodology ESAC is currently conducting a larger study with 50 hospitals that will provide longitudinal data linked with point prevalence data about prescribed doses and details about hospital characteristics.

5.7 Conclusion

This study required considerable time and effort to allow raw data collection, validation in different phases of the project, and processing and analysis. This precision can hardly be applied to future projects with a larger number of hospitals or be applied to all of Europe. The ATC/DDD method has been used for more than four decades. Ten years ago the European Union passed agreements and laws on the standardised method of antimicrobial consumption surveillances. Yet, the national networks are established only in a few countries. Additionally, the European Union funded studies like ESAC for continuous data collection and monitoring. In this and similar projects, countries participate on a voluntary basis and the funding for projects is not enough to pay for data collection of the participating countries even for a study like this that included one hospital per country. The EU agreements on continuous surveillances on antimicrobial

use with standardised methods will not be feasible across the rest of Europe until countries agree on a budget allocation for the establishment of national networks for antibiotic use in hospitals. The reader will recall from earlier in this chapter the problems associated with pharmacy stock databases and different data collection methods for clinical activity variables. Therefore, central, preliminary data processing and analysis at national level would provide greater validity.

In this study the extent to which using a similar numerator of use, DDD, can allow exploration of the effects of an additional denominator of clinical activity was proved.

The strengths of this study are implementing standardised methods to collect and analyse longitudinal data from multiple countries with very different healthcare systems. The methods have addressed several of the weaknesses identified in previous studies. [192] Furthermore, new methods for statistical analysis of changes over time using both slope and intercept, and for time series analysis of antibacterial use was developed. In the other method - scaled trends in simple regression - it became feasible to compare the trends between hospitals and between different variables.

The study described limitations in using one denominator of clinical activity and the overestimation caused by occupied bed days.

Hospitals varied widely in their trends of use and clinical activity during the study period. Some of the variations will be explained in chapter 7 and 8 when the point prevalence survey in the same hospitals and hospital characteristics will be discussed. This study could suggest a method for categorising hospitals.

The results can be transferred to cross-sectional surveys, studies on antibiotic use and resistance in secondary care and also use of other medicines in secondary care. Weaknesses of this study are that it includes one hospital per country and only 18

hospitals in total. This is too small a sample size to explore determinants of change in antibacterial use. Having established the methodology, ESAC is currently conducting a larger study with 50 hospitals that will provide longitudinal data, point prevalence data and details about hospital characteristics.

CHAPTER SIX: ESAC LONGITUDINAL SURVEY 2, TIME SERIES ANALYSIS OF TOTAL, PARENTERAL AND BROAD-SPECTRUM ANTIBACTERIAL USAGE

6.1 Background

This chapter is an additional study to the main components of the ESAC-2 hospital care sub-project. The aim is to provide more in-depth analysis on longitudinal data to compare indicators of hospital antibiotic use. Parenteral antibacterials, Fluoroquinolones and third generation Cephalosporins (CQ antibiotics) were selected for the study. These are antibiotics associated with higher cost and risk of adverse effects, including for CQ antibiotics a greater risk of collateral damage (*C difficile* infection and microbial resistance). Time series data on total use and use of selected antibacterials from each of the 18 hospitals were compared in this study. The study focused on mean annual change in each indicator as the outcome measure.

6.2 Aim

To develop and validate more meaningful indicators of hospital antibiotic use that can be easily extracted from routine longitudinal data and, when added to indicators developed from point prevalence surveys, can build a set of core indicators that can be used to compare antimicrobial prescribing in hospitals in European countries.

6.3 Research question

Are the same time trends present in use of total antibiotics, parenteral antibiotics and antibiotics with high risk of collateral damage?

6.4 Introduction

In addition to total antibiotic use, two other indicators of use were identified: firstly, parenteral antibiotics and secondly, use of third generation Cephalosporins (J01DD) and

Fluoroquinolones (J01MA). The rationale for these additional indicators was that they are key targets for antimicrobial stewardship programmes in hospitals.[46, 49] Unnecessary parenteral antibiotic use exposes patients to additional risk and hospitals to additional costs without clinical benefit.[25, 46, 273] Use of third generation Cephalosporins and Fluoroquinolones is associated with the prevalence of antimicrobial resistant bacteria (e.g. MRSA and multiple resistant gram negative bacteria) and *C difficile* infection [46, 273-275]. Interventions to reduce the use of these drugs have been associated with a significant reduction in the prevalence of antimicrobial resistance and *C difficile.*[276] A seven-year survey (1980-86) in France revealed significant correlation between an increase in antibiotic use and a decrease in antibiotic susceptibility, especially for third generation Cephalosporins.[64] A nine-year follow-up study in the adverse effect of parenteral treatment in chronic bone infections (CBI), that often requires prolonged parenteral antimicrobial therapy, showed that at least one- third of patients with CBI experienced adverse effects that were related to both the device used for IV administration and the antibiotics that were administered. [277]

6.5 Methods

In Chapter Five, the methods for collection, validating and processing and analysing raw pharmacy stock data were described. In the current chapter, total antibacterial use, use of parenterals, and use of third generation Cephalosporins plus Fluoroquinolones during the study period were extracted from the data for each of the hospitals. Each hospital was given a number consistent with the numbers in the point prevalence and longitudinal surveys in Chapters Five, Seven and Eight. Three variables were constructed for each of the hospitals: Total use (T), Parenteral use (P) and the sum of use of third generation Cephalosporins and Fluoroquinolones (CQ), so the database included 54 (3× 18) times series.

Use of antibacterials was measured in DDDs as defined by the WHO Collaborating Centre for Drug Statistics Methodology.[265] Data were not scaled by clinical activity denominator because the changes in any clinical activity variable should be equal and consistent for all three variables in each of the hospitals and any adjustment would be disregarded in a regression analysis of time series. Hospitals were categorised based on findings from individual hospitals. No comparison was performed between hospitals for the three series (T, P, and CQ).

6.5.1 Statistical analysis

The following steps were taken to prepare data for time series regression

- Plot the data
- Identify the outliers and structural breaks from plots and corresponding data
- Contact the hospitals to find if there is any explanation for outliers and structural breaks
- Correct the outliers in line with responses from those hospitals that could identify and correct their databases.
- Run the statistical tests for stationarity and trend
- Test if the outliers and structural breaks exist after removing seasonality
- Use the criteria Q3 ± (3* IQR) limit (inter-quartile) to find the far outliers and remove them if they were first or last data point and when they were in the middle of times series replace with the average of the data points immediatly before and after the outlier.
- Use dummy variable for structural breaks

Details of the above steps are described as in the following.

Prior to a time series analysis, 54 series were tested for stationarity and trend using two statistical tests. In time series analysis, if the data are not stationary there is evidence of a unit root that may happen in the presence of a trend in the series. [197] Data series were tested for stationarity using two statistical tests: Phillips-Perron (PP) and Kwiatkowski-Phillips-Schmidt-Shin (KPSS) tests.[202, 278] The two test results were not expected to be consistent with each other. A time series is stationary if it exhibits a reversion around a constant long-run mean; has a finite variance that is time invariant; and has a theoretical correlogram that diminishes as the lag length increases. [195] While the PP test examines the reversion around a constant long-run mean, the KPSS test differs in that the productivity series is assumed to be (trend) stationary under the null hypothesis.[279] The KPSS test is used for testing the null hypothesis that a time series is stationary around a deterministic trend. The Phillip-Perron test checks the null hypothesis that a time series has a unit root against a stationary alternative. [195, 279] The PP test and KPSS tests can be compared in the following general interpretation:

"Being declared guilty (PP test) is not the same thing as not being declared innocent (KPSS test)".

Box-plot graphs and statistical tests were used to identify outliers in the series. For this, the inter-quartile range (IQR), first (Q1) and third quartiles (Q3) were calculated. The far outlier was defined as a data point that lies outside the Q3 ± (3* IQR) limit. Near outliers were data points that lay outside the Q1± (1.5*IQR) limits.[280] The far outliers were replaced with the average of immediate data points before and after the outlier. If the far outlier was the first or last data point, it was deleted. To deal with near outliers, if they existed in a series, the data were de-seasonalised to find whether or not the near outliers were in fact a seasonal pick and when they were not, they also replaced with the average value of immediate data points before and after the near outliers. Structural

dummies were assigned to those series with one or more sudden changes. Time series analysis was conducted for 54 time series. Each of the series was regressed over trend and seasonal and structural dummies. [195]

In case of a structural break and to understand what the outcome would be a dummy variable was used, which can affect both the intercept and the slope coefficients. If D is the assumed dummy variable for the structural break, it would be equal to 1 and 0 otherwise.

$$D = \begin{cases} 0 & for \quad t = 1, \dots, s \\ 1 & for \quad t = s+1, \dots, T \end{cases}$$ [195] (6.1)

The following regression model was used.

$$Y_t = B_1 + B_2 X_{2t} + B_3 D_t + B_4 D_t X_{2t} + u_t$$ [195] (6.2)

B_3D_t and B_4D_t were the interaction terms between constants and trends coefficients respectively. The significance of B3Dt and B4Dt coefficients could also cautiously determine whether the structural break was real or they had been picked up by incorrect graphical interpretations.

The series were regressed on trend (t) seasonal dummy variables with January as the reference month. ARMA components were used to correct serial autocorrelation of residuals, where appropriate. Selection of the best fitted model, as described in Chapter 2, was based on the Jarque-Bera test for normality of residuals and Q statistics and Breusch-Godfrey Lagrange Multiplier statistics (B-G LM Statistic) for autocorrelation between residuals, see example in Figure 5.5 in Chapter 5. For times series analysis, evaluation of the model based on R-Squared is misleading. Even badly specified time series equations can give R2 of 0.999. [195] Trends or change per month for the three series: total, parenteral and third generation Cephalosporins plus Fluoroquinolones for each of the hospitals cannot be compared directly, firstly because the two latter series

are fractions of total use and secondly, because a small trend built on a large constant may exhibit the same change with another series with a sharp trend with a low constant. From the best fitted regression model and where the trend was significant, the slope trend and constant (intercept) values were used to scale the change using the intercept. The mean annual percentage change was calculated using the formula below which was created in Chapter Five to scale the trends with constant and presented as a percentage of mean annual change.

$$\% \Delta \text{ Variable} = [(\textit{Slope} * 12)/ \textit{Intercept}] * 100 \qquad \text{(LS 5.3)}$$

The pooled statistical outcomes for all hospitals were explored for correlation, first between changes in total and parenteral use, and second between changes in total and third generation Cephalosporins plus Fluoroquinolones. The correlations were calculated regardless of whether the change values were significant.

All statistical analyses were performed with EViews 6 software (QMS, Irvine, CA, USA).

6.6 Results

6.6.1 Description and statistical analysis of time series

Time series plots for Total (T), Parenteral (P) and third generation Cephalosporins plus Fluoroquinolones (CQ) are presented in Tables 6.1 to 6.3. The series vary across hospitals with respect to trend, seasonality, instability and autoregressive patterns. In some series, raw data series exhibit clear upward trends (H7P, H15CQ) or clear downward trends (H1T, H9T, H9CQ). However, several series do not exhibit any clear time trend (H13T, H16T, H8P, H13P and H13CQ).

The results of 108 tests of stationarity with PP and KPSS test statistics for each series showed that the tests do not have similar powers to detect the trend and that the KPSS

test is more powerful. An example of two test statistics for the H2T series with a clear trend is described in Table 6.4a. Prior to the tests where the constant and trend are included in both, the series was tested on constant only and the KPSS showed non-stationarity in favour of having a trend while the PP test did not. This discrepancy was the same with most of the other series with or without trend, in the raw data series. Some series had structural breaks after removing outliers from some of them, where appropriate, based on the criteria that were explained in the methods section. These series were: H4T, H4P, H5T, H5P, H5CQ, H8T, H8CQ, H9CQ, H12T, H12P, H14P, H14CQ, and H17CQ (Tables 6.1 to 6.3). In Table 6.4b two tests for stationarity are shown for H12T. Both tests are in favour of non-stationarity with weak Durbin-Watson test statistics. Furthermore the tests suggest a positive trend while later in regression analysis it was found that this series contains a significant negative trend if the structural break dummy is being included. Therefore, in the presence of breaks, unit root tests are invalid.

The regression of time series was conducted for all series. The output for 54 of the series was too long to be included in this thesis. For one series, the regression model is provided and described in Table 6.5.

In hospital 14 for H14T, the model with best fit was usage measured in DDDs regressed over time squared (t^2) and time (t). Therefore, a graph of the regression line was polynomial. The curvature component was calculated and incorporated to extract time trend to allow the comparison to be comparable with two other series in the same hospitals,[281] (and with advice through personal communication with Dr Simon Ogston, Department of Public Health, University of Dundee).

Table 6.1: Times series data on total use of antibacterials (T) by hospital number

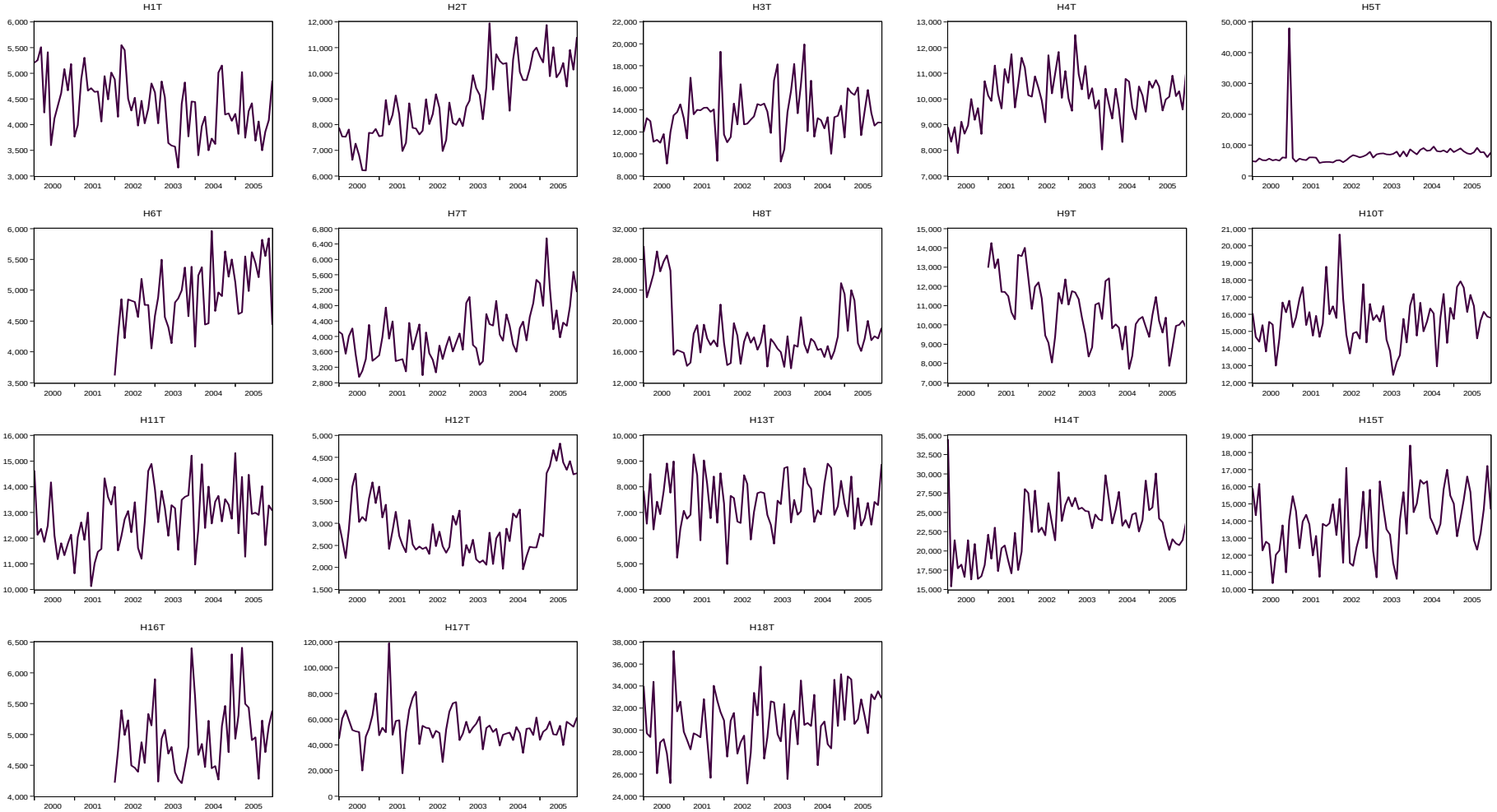


Table 6.2: Times series data on use of parenteral antibacterials (P) by hospital number

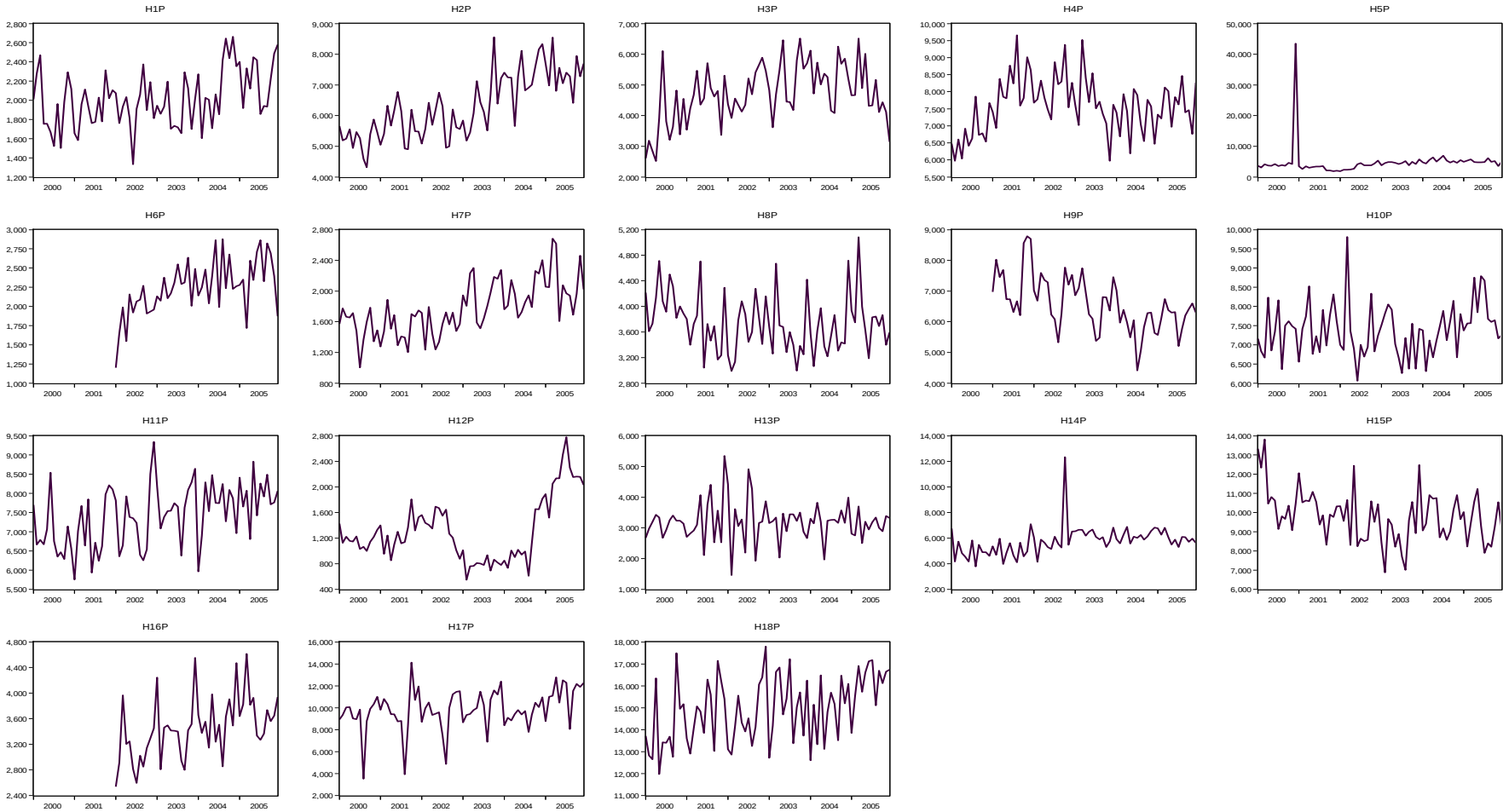


Table 6.3: Times series data on use of Cephalosporins and Fluoroquinolones (CQ) by hospital number

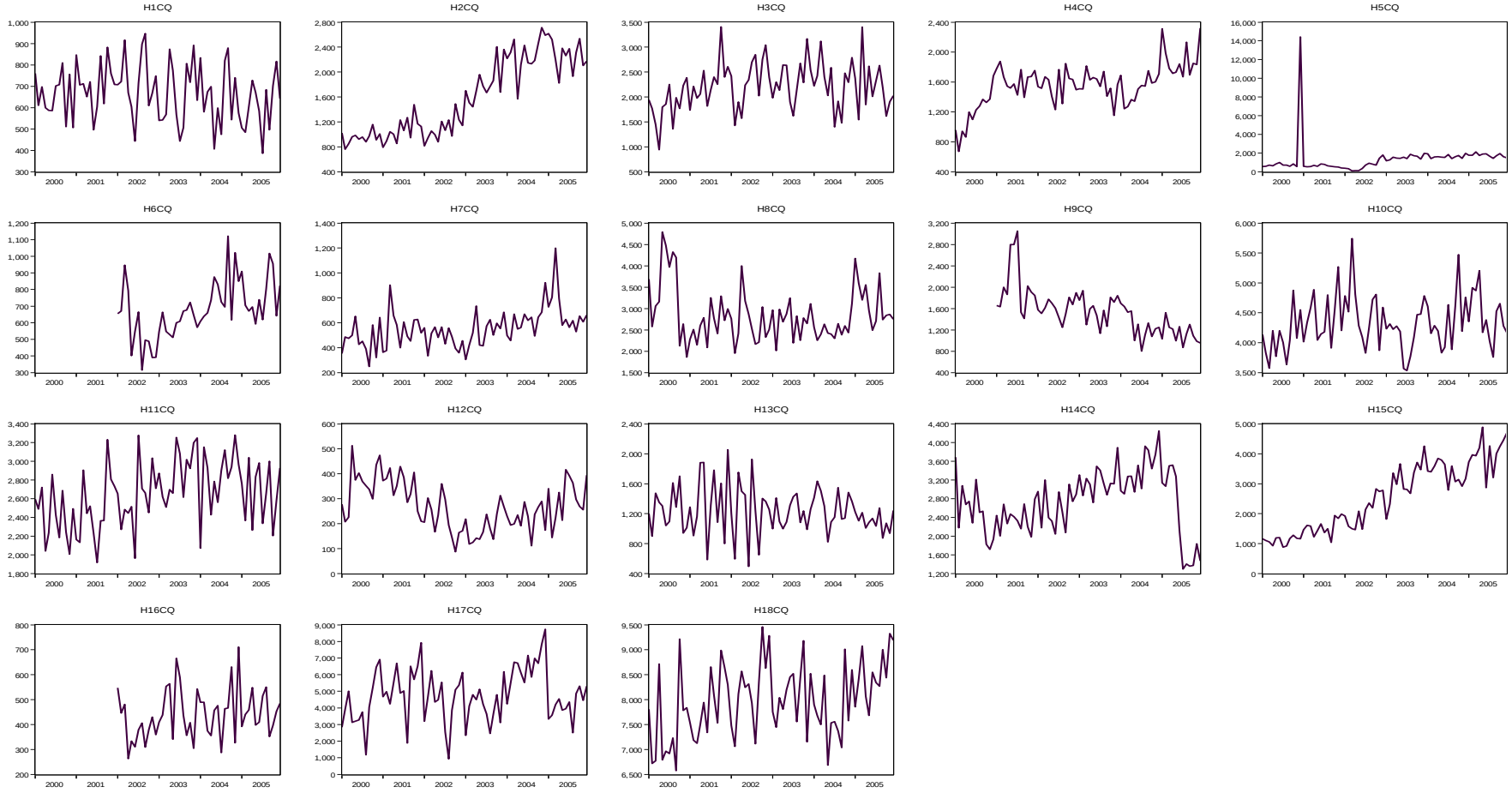


Table 6.4a and 6.4b: Examination of Phillips-Perron and KPSS tests for one series with obvious trend, and another with structural break

Null Hypothesis: H2T has a unit root				
Exogenous: Constant, Linear Trend				
Bandwidth: 2 (Newey-West using Bartlett kernel)				
			Adj. t-Stat	Prob.*
Phillips-Perron test statistic			**-6.70**	**0**
Test critical values:	1% level		-4.09	
	5% level		-3.47	
	10% level		-3.16	
*MacKinnon (1996) one-sided p-values.				
Residual variance (no correction)				576698
HAC corrected variance (Bartlett kernel)				558317
Phillips-Perron Test Equation				
Dependent Variable: D(H2T)				
Method: Least Squares				
Sample (adjusted): 2000M02 2005M12				
Included observations: 71 after adjustments				
	Coefficient	Std. Error	t-Statistic	Prob.
H2T(-1)	-0.79	0.12	-6.72	0
C	5,425.87	829.83	6.54	0
@TREND(2000M01	45.93	7.96	5.77	0
R-squared	0.40	Mean dependent var		49.67
Adjusted R-squared	0.38	S.D. dependent var		987.52
S.E. of regression	775.98	Akaike info criterion		16.19
Sum squared resid	40945579	Schwarz criterion		16.28
Log likelihood	-571.65	Hannan-Quinn criter.		16.23
F-statistic	22.68	Durbin-Watson stat		**2.01**
Prob(F-statistic)	0			

Null Hypothesis: H2T is stationary				
Exogenous: Constant, Linear Trend				
Bandwidth: 3 (Newey-West using Bartlett kernel)				
				LM-Stat.
Kwiatkowski-Phillips-Schmidt-Shin test statistic				**0.098**
Asymptotic critical values*:		1% level		0.216
		5% level		0.146
		10% level		0.119
*Kwiatkowski-Phillips-Schmidt-Shin (1992, Table 1)				
Residual variance (no correction)				608717
HAC corrected variance (Bartlett kernel)				870296
KPSS Test Equation				
Dependent Variable: H2T				
Method: Least Squares				
Sample: 2000M01 2005M12				
Included observations: 72				
	Coefficient	Std. Error	t-Statistic	Prob.
C	6,923.58	184.58	37.51	0
@TREND(2000M01)	56.50	4.49	12.59	0
R-squared	0.69	Mean dependent var		8929.47
Adjusted R-squared	0.69	S.D. dependent var		1419.75
S.E. of regression	791.27	Akaike info criterion		16.21
Sum squared resid	43827639	Schwarz criterion		16.28
Log likelihood	-581.65	Hannan-Quinn criter.		16.24
F-statistic	158.58	Durbin-Watson stat		**1.56**
Prob(F-statistic)	0			

a) H2T- The Phillips-Perron t statistics, -6.70, is lower than critical values, the null hypothesis is rejected and the series are trend stationary. In left table, the KPSS t statistics, 0.98, is lower than critical values therefore the null hypothesis is rejected in favour of non-stationarity. However the Durbin-Watston stat for KPSS test shows autocorrelation of the residuals should be corrected for in regression of the series. Two tests produced different results.

Null Hypothesis: H12T has a unit root				
Exogenous: Constant, Linear Trend				
Bandwidth: 2 (Newey-West using Bartlett kernel)				
			Adj. t-Stat	Prob.*
Phillips-Perron test statistic			**-£2.94**	**£0.16**
Test critical values:	1% level		-£4.09	
	5% level		-£3.47	
	10% level		-£3.16	
*MacKinnon (1996) one-sided p-values.				
Residual variance (no correction)				234780
HAC corrected variance (Bartlett kernel)				208816
Phillips-Perron Test Equation				
Dependent Variable: D(H12T)				
Method: Least Squares				
Sample (adjusted): 2000M02 2005M12				
Included observations: 71 after adjustments				
	Coefficient	Std. Error	t-Statistic	Prob.
H12T(-1)	-0.255478	0.08	-3.09	0.0029
C	656.2011	253.64	2.59	0.0118
@TREND(2000M01	3.206735	2.92	1.10	0.2767
R-squared	0.13	Mean dependent var		16.14
Adjusted R-squared	0.10	S.D. dependent var		521.89
S.E. of regression	495.11	Akaike info criterion		15.29
Sum squared resid	16669395	Schwarz criterion		15.38
Log likelihood	-539.75	Hannan-Quinn criter.		15.33
F-statistic	4.89	Durbin-Watson stat		**2.37**
Prob(F-statistic)	0.01			

Null Hypothesis: H12T is stationary				
Exogenous: Constant, Linear Trend				
Bandwidth: 6 (Newey-West using Bartlett kernel)				
				LM-Stat.
Kwiatkowski-Phillips-Schmidt-Shin test statistic				**0.21**
Asymptotic critical values*:		1% level		0.22
		5% level		0.15
		10% level		0.12
***Kwiatkowski-Phillips-Schmidt-Shin (1992, Table 1)**				
Residual variance (no correction)				508299
HAC corrected variance (Bartlett kernel)				2244012
KPSS Test Equation				
Dependent Variable: H12T				
Method: Least Squares				
Sample: 2000M01 2005M12				
Included observations: 72				
	Coefficient	Std. Error	t-Statistic	Prob.
C	2689.42	168.668	15.94505	0
@TREND(2000M01)	8.01	4.10025	1.952611	0.0549
R-squared	0.05	Mean dependent var		2,973.64
Adjusted R-squared	0.04	S.D. dependent var		737.25
S.E. of regression	723.06	Akaike info criterion		16.03
Sum squared resid	36597549	Schwarz criterion		16.10
Log likelihood	-575.16	Hannan-Quinn criter.		16.06
F-statistic	3.81	Durbin-Watson stat		**0.52**
Prob(F-statistic)	0.05			

1-

1-b) H12T- This series contains one significant structural break. The Phillips-Perron statistics, -2.94, is bigger than critical values so the null hypothesis is not rejected and the series has a unit root. But it shows a positive trend and highly correlated residuals. The KPSS test stat, 0.21, is between 1% and 5% critical values so the null hypothesis is not rejected and the series are stationary. The estimated trend is 8.01 and the Durbin-Watson stat is far from 2. The trend with both tests are positive, however later in regression of time series it will be found that the trend is negative. Therefore, none of the tests give valid results for structural break. Time series regression after this test showed that the trend was negative

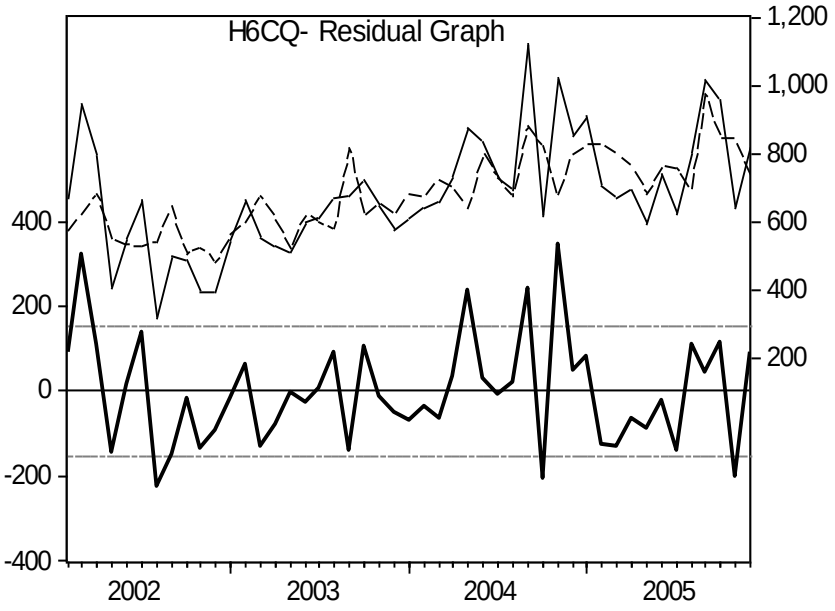
Table 6.5: An example for regression of time series on trend, hospital 6 Cephalosporins and Fluoroquinolones.

Dependent Variable: H6CO
Method: Least Squares
Sample (adjusted): 2002M02 2005M12
Included observations: 47 after adjustments
Convergence achieved after 4 iterations

	Coefficient	Std. Error	t-Statistic	Prob.
C	359.1840	155.5380	2.309301	0.0273
@TREND	6.935118	2.509847	2.763164	0.0093
DM_2	2.704457	99.30769	0.027233	0.978400
DM_3	38.45616	115.9440	0.331679	0.742200
DM_4	15.78228	120.8483	0.130596	0.896900
DM_5	-82.84906	122.2737	-0.677570	0.502800
DM_6	-5.704589	122.6196	-0.046523	0.963200
DM_7	-37.82654	122.6258	-0.308471	0.759700
DM_8	-77.69633	122.4768	-0.634376	0.530200
DM_9	121.5047	122.0662	0.995400	0.326800
DM_10	-17.16660	120.8437	-0.142056	0.887900
DM_11	-45.07052	116.9856	-0.385266	0.702500
DM_12	-67.52200	104.1202	-0.648500	0.521100
AR(1)	0.326028	0.163657	1.992137	0.054700

R-squared	0.438732	Mean dependent var	679.7697
Adjusted R-squared	0.217626	S.D. dependent var	172.9652
S.E. of regression	152.9910	Akaike info criterion	13.14074
Sum squared resid	772405.7	Schwarz criterion	13.69185
Log likelihood	-294.8074	Hannan-Quinn criter.	13.34812
F-statistic	1.984263	Durbin-Watson stat	2.102717
Prob(F-statistic)	0.055674		

B_G LM Statistic:	1.019915	Prob. F(6,27)	0.433600
Q Statistic	5.165800	Prob. Chi-	0.396000



Dm_2 to Dm_12 are monthly seasonal dummies. The series has a significant time trend. The trend coefficient is 6.94 with standard error of 2.51. The Jarque-Bera equals to 3.33 with P-value of 0.19 so the residuals are normally distributed. Autocorrelation tests Q statistics and Breusch-Godfrey Lagrange statistics (B_G LM Statistic) with 6 lags which generally applies to monthly data are not associated with significant probability of chi-squared so there is no autocorrelation in the residuals.

Table 6.6 and Figure 6.1 summarise all statistical analysis for the multiple time series analysis followed by incorporating the trend and constant components into mean annual changes for the three series in each of the hospitals

6.6.2 Comparison of trends in the three indicators of antibiotic use

The research question was "Are the same time trends present in use of total antibiotics, parenteral antibiotics and antibiotics with high risk of collateral damage?" In order to answer this question hospitals were grouped firstly for the changes in parenteral use versus total use and secondly for changes in use of CQ antibacterials versus total use.

Comparison of average annual changes in all three indicators

Average annual changes in total antibacterial use, measured in DDDs, were compared with changes in parenteral antibacterials and with the sum of Fluoroquinolones (J01MA) and third generation Cephalosporins (J01DD) for each hospital.

In hospitals 1, 4, 9, 12 and 17, total use decreased from -2% to -4.7% per year. The change for hospital 17 was not significant. In thirteen other hospitals, total use increased from 0.1% in hospital number 13 to 10.4% in hospital number 2. The increasing rate was not significant in hospitals 3, 10, 13 and 17. In general, total use increased in 50% of the hospitals, decreased in 22%, and remained unchanged (insignificant change) in 28% (Table 6.6 and Figure 6.1).

Use of parenteral antibacterials decreased in five hospitals (4, 8, 9, 13, and 15) from -0.5% to -4.5% but this change was significant only in hospitals 4, 9 and 15. In thirteen other hospitals there were increasing changes from 0.8% to 17.7% and the upward change was significant in 12 hospitals. In total for fifteen (83%) hospitals the changes were significant, increasing in 67% and decreasing in 17%. In 17% of hospitals (hospitals 8, 10 and 13) there was no significance level of change.

The use of third generation Cephalosporins plus Fluoroquinolones decreased in five hospitals (hospital numbers 1, 9, 10, 12 and 13) from -0.28% to -7.6% but it was significant only for two hospitals. In thirteen other hospitals, use of these antibacterial groups increased from 1.4% to 96.1%. The upward change was significant in eight hospitals. In total, in 11% of hospitals the use decreased, while in 44.5% use increased and in 44.5% it remained unchanged (insignificant change). (Table 6.6 and Figure 6.1).

Difference between change in total use and change in the other two indicators

To compare the change values in each hospital between parenteral and total use and between uses of third generation Cephalosporins plus Fluoroquinolones (CQ), changes in total use were deducted from the other two indicators: ΔP-ΔT and ΔCQ-ΔT.

The differences were considered positive (>0) if:

- The increases in P or CQ were more than increase in T or,
- ΔP or ΔCQ was positive while ΔT was constant or was not significant or,
- ΔP or ΔCQ were positive while ΔT was negative.

The differences were considered negative (<0) if:

- ΔT increase more than ΔP or ΔCQ or,
- ΔT was positive while ΔP or ΔCQ were negative or,
- ΔT was positive and ΔP or ΔCQ was constant or insignificant or,
- ΔT was negative but less than negative values for ΔP or ΔCQ.
- The differences were considered as nearly equal (≈) if there were no change or no significant change in ΔT and ΔP or ΔCQ.

The overall interpretation of differences and grouping the hospitals are presented in Table 6.7 (A & B).

Correlation between change in total use and each of two antibacterial groups

There were non-significant correlations between changes in total use and change of use of parenteral antibacterials across the hospitals either for all data regardless of level of significance (correlation coefficient: 0.4070, *P*-value: 0.09) or for thirteen hospitals with significant changes in 2 variables (correlation coefficient 0.41, *P*-value: 0.16). There was also non-significant correlation between changes in the total use and the changes in use of third generation Cephalosporins plus Fluoroquinolones for all hospitals (correlation coefficient: 0.388, P-value: 0.11) and for eight hospitals with significant changes in both variables (correlation coefficient: 0.18, P-value: 0.66).

6.7 Discussion

This was the first study to compare time trends for three indicators of antibacterial use in multiple hospitals. Most previous longitudinal studies of hospital antibiotic use were focused on a single hospital and no previous study used statistical analysis to compare trends. [282-284]

The raw pharmacy stock data were assigned to ATC/DDDs by the central team in Dundee, with much time and effort put into data validation through repeated communication with data providers. Nonetheless the local data providers could often not diagnose the source of irregular behaviour patterns of their data such as outliers and one or more abrupt changes. Accordingly, a limitation of this study was that 13 of the 54 series had abrupt change in level or presence of outliers even after checking of data with local providers (Tables 6.1-6.3). This highlights a key problem of this kind of comparative analysis that routine data from different institutions and countries can be variable in ways that are difficult to explain or resolve. The data should therefore be interpreted cautiously. It is important to recognise that time series analysis and its

techniques are mainly applied to social and economic data for which there is supporting historical information about the reasons for irregular time series behaviours. In contrast for this study hospitals were unable to provide information to explain several outliers or sudden changes and breaks in the data. The availability of data about characteristics of hospitals that may explain differences between them is explored further in Chapter 8.

In some series, there were variations from month to month in pharmacy stock data. It may be that pharmacy stock data do not reflect changes in actual usage over time. Variations in drug dispensing systems and the impact of a ward buffer from month to month may explain some of the time trends observed in this study. This study benefits from a robust, multistep statistical method based on monthly pharmacy stock data. The statistical analysis of the time series used in this study did correct some of the irregularity in the time series and used published methods to extract the time trend for statistical comparison. Nonetheless, the validity of methods for extraction of the trend component for a time series is still a matter of discussion between economists and social scientists.

Despite these caveats the statistical analysis did answer the research question and showed that there was little relationship between changes in total antibiotic use and use of either parenteral or CQ antibiotics. Importantly, the 18 hospitals included examples with significant increases or decreases in each of the three indicators. In 67% (11) of the hospitals change in use of parenteral antibacterials was greater than change in total use, in 28% (5) it was smaller and in 11% (2) of the hospitals both were constant (Table 6.6). Similarly in 56% (10) of the hospitals change in use of CQ antibiotics was increasing more than total use, in 28% (5) it was decreasing more and in 3% (3) the speed of exposure was constant. Therefore in the majority of hospitals changes in total antibiotic use masked the changes in the use of either parenteral antibacterials or CQ antibiotics.

Finally, correlation analysis was used to compare changes between pairs of indicators for all 18 hospitals. These showed non-significant correlations. Moreover any apparent correlation should be interpreted with caution because it may be due to the influence of a small number of extreme data points.

6.8 Conclusion

With hindsight it could be said that the results of this analysis are not surprising however, it is well documented in this study. I have shown that time series analysis can be used to compare changes in use of different antibiotics within a hospital and to compare trends in the same antibiotics between hospitals. With running 54 pairs (108) KPSS and PP tests for trend and stationarity the inconsistency between these two tests was confirmed as it was suggested in literature.[279] The results show clearly that potentially important changes in use of either parenteral or CQ antibiotics may not be apparent from changes in total use. The study had limitation of data validity for all times series. In this chapter a series of methods and techniques used to minimise these problems. However, my results imply that routine monitoring needs better data systems. Pharmacy databases need to be regularly checked for unexpected values in the way that I established for Tayside university hospitals. Resourcing of data checking at local level is an essential first step to making valid national and international comparisons.

Table 6.6: Percentage of mean annual changes for Total (T), Parenteral (P) and third generation Cephalosporins plus fluoroquinolones (CQ) for each of the hospitals (H). Significant changes are highlighted.

Hospital & series	%Change	Confidence Intervals	*P* value	Hospital & series	% Change	Confidence Intervals	*P* value
H1T	-2.97	-4.71, -1.50	<0.001	H10T	0.75	-0.46, 1.79	0.22
H1P	3.18	1.55, 4.46	<0.01	H10P	0.80	-0.52, 1.91	0.22
H1CQ	-1.85	-5.67, 0.84	0.21	H10CQ	-0.28	-3.10, 1.96	0.82
H2T	10.42	9.46, 11.19	<0.001	H11T	1.70	0.62, 2.65	<0.01
H2P	9.95	8.66, 10.93	<0.001	H11P	3.00	1.79, 4.01	<0.001
H2CQ	49.33	39.56, 79.80	<0.001	H11CQ	3.14	1.40, 4.50	<0.01
H3T	1.93	-0.37, 3.65	0.10	H12T	-4.34	-8.99, -0.86	0.01
H3P	4.97	2.51, 7.02	<0.001	H12P	17.72	14.26, 19.28	<0.001
H3CQ	2.76	-0.66, 4.98	0.10	H12CQ	-4.92	-19.91, 2.21	0.23
H4T	-1.61	-3.07, -0.35	0.02	H13T	0.01	-1.35, 1.10	0.99
H4P	-3.10	-5.41, -1.17	<0.01	H13P	-0.48	-3.49, 1.70	0.70
H4CQ	3.40	-1.54, 6.67	0.16	H13CQ	-2.42	-4.27, -1.17	<0.001
H5T	12.20	11.05, 13.03	<0.001	H14T	4.39	2.86, 5.83	<0.001
H5P	11.73	9.53, 13.09	<0.001	H14P	4.77	0.74, 7.68	0.03
H5CQ	45.27	36.75, 64.81	<0.05	H14CQ	10.83	8.88, 12.13	<0.001
H6T	5.44	3.68, 6.70	<0.001	H15T	2.51	1.23, 3.58	<0.001
H6P	12.20	9.57, 13.68	<0.001	H15P	-2.49	-4.42, -0.88	<0.01
H6CQ	23.17	21.37, 44.52	<0.01	H15CQ	96.14	61.46, 130.80	<0.001
H7T	6.36	4.77, 7.60	<0.001	H16T	2.57	0.24, 4.39	<0.05
H7P	9.26	8.25, 10.03	<0.001	H16P	6.77	7.06, 6.55	<0.001
H7CQ	9.61	2.32, 12.83	<0.05	H16CQ	4.58	-32.96, 42.13	0.17
H8T	2.58	-0.22, 4.72	0.07	H17T	-2.01	-6.42, 1.13	0.24
H8P	-0.92	-4.29, 1.66	0.52	H17P	4.50	1.75, 6.54	<0.01
H8CQ	4.07	0.59, 6.75	0.02	H17CQ	19.34	-38.22, 76.90	0.20
H9T	-4.74	-6.35, -3.34	<0.001	H18T	1.10	0.22, 1.88	<0.05
H9P	-4.51	-6.17, -3.06	<0.001	H18P	2.55	1.50, 3.45	<0.001
H9CQ	-7.61	-10.72, -5.09	<0.001	H18CQ	1.39	-1.24, 3.46	0.28

Table 6.7: Overall interpretation of difference in change between indicators

A: changes in total antimicrobial versus changes in parenteral antibacterial use.

Interpretation of change in exposure to parenteral antibacterials compared with total antibacterials	Outcome	Number of hospitals (% form total hospitals)	Hospital Numbers
Exposure was bigger	ΔP>ΔT	11(61%)	1, 3,6,7,9,11,12, 14,16,17,18
Exposure was smaller	ΔP<ΔT	5 (28%)	2, 4, 5, 8,15
Exposure was equal	ΔP≈ΔT	2 (11%)	10, 13

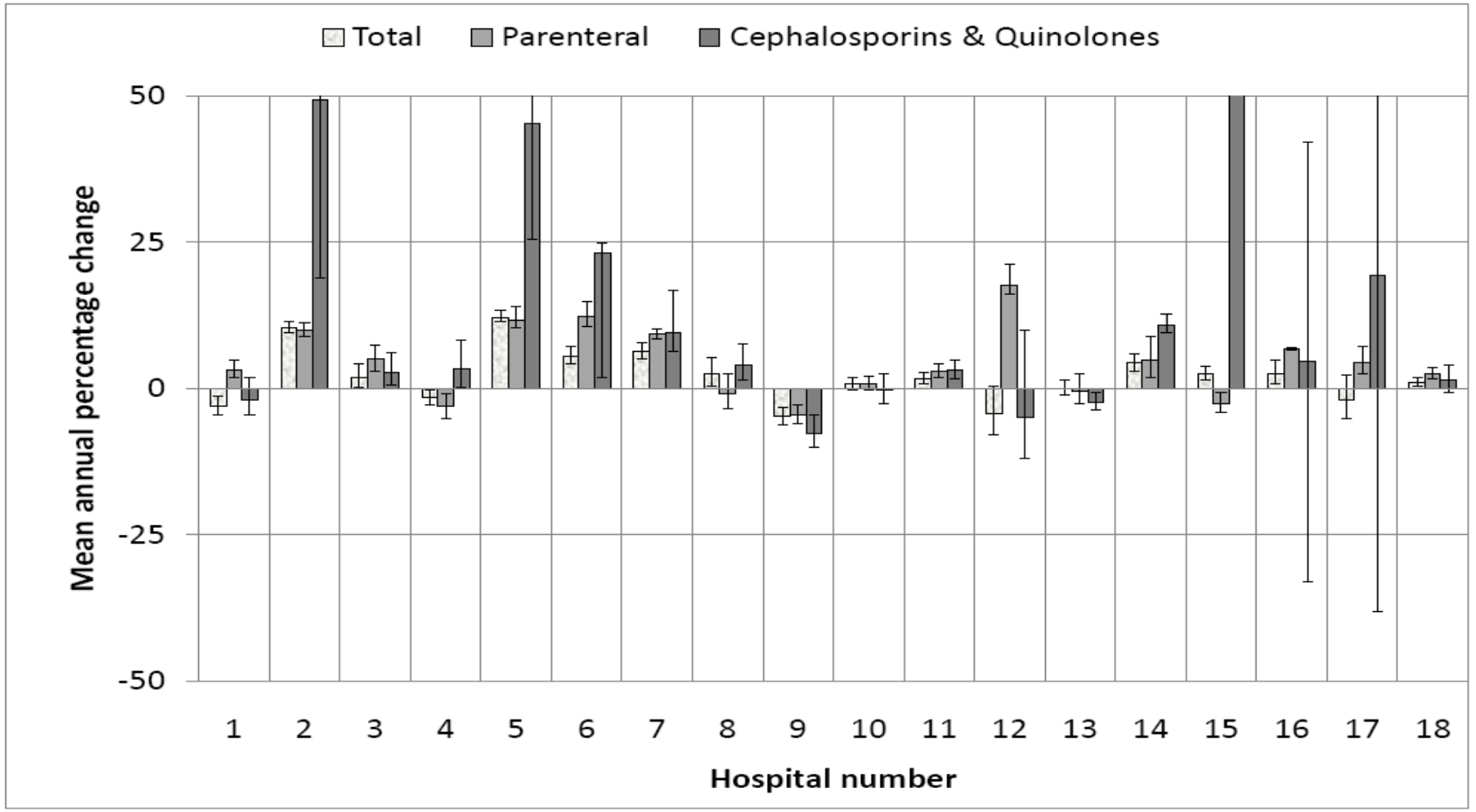
Δ: change, P: Parenteral antibacterials, T: total antibacterials

B: Changes in total antimicrobial use versus changes in third generation Cephalosporins and Fluoroquinolones (CQ) use.

Interpretation of change in exposure to parenteral antibacterials compared with total antibacterials	Outcome	Number of hospitals (% form total hospitals)	Hospital Numbers
Exposure was bigger	ΔCQ>ΔT	10 (56%)	1,2,4,6,7,8,11,12,14,15
Exposure was smaller	ΔCQ <ΔT	5 (28%)	5,9, 13,16,18
Exposure was equal	ΔCQ ≈ΔT	3(16%)	3,10,17

Δ: change, CQ: third generation Cephalosporins and Fluoroquinolones, T: total antibacterials

Figure 6.1: Mean annual percentage of change in defined daily doses (DDD) of total antibiotics, parenteral antibiotics and 3rd generation cephalosporins plus fluoroquinolones with 95% confidence intervals



CHAPTER SEVEN: THE EUROPEAN SURVEILLANCE OF ANTIMICROBIAL CONSUMPTION (ESAC) POINT PREVALENCE SURVEY OF ANTIBACTERIAL USE IN 20 EUROPEAN HOSPITALS IN 2006

7.1 Background

The most important advantage of cross-sectional studies is that can usually be done rapidly and since there is no follow-up, fewer resources are required to run the study. Cross- sectional studies are the best way to determine prevalence and are useful at identifying associations that can then be more rigorously examined using a cohort study or randomised controlled study.[285] As a result, point prevalence surveys have been used to document antibacterial use in hospitals for over 20 years. This chapter focuses on standardising the method for surveillance of antibacterial use in hospitals from different healthcare systems and identifying areas for quality improvement.

7.2 Introduction

Point Prevalence Surveys (PPS) can provide detailed clinical data to supplement information available from aggregated pharmacy stock databases, to provide a broader perspective on practice profile in studies of hospital drug utilisation. This clinical evidence can be used to improve guidelines and quality measurements for improvement of clinical practice (Figure 1.1[6] in Chapter 1). The value and limitations of Point Prevalence Surveys of hospital antimicrobial use was discussed in Chapter One of this thesis. Despite the limitation of previously published evidence reviewed in Table 1.2 of Chapter 1, these studies together with numerous publications produced from other kinds of hospital record based studies, have provided evidence of existing practice and

contributed to improvement of methods and measures. Data about antimicrobial use have been also collected in surveys of hospital acquired infections. For example, a national survey of 11,608 inpatients in all acute hospitals in Scotland in 2005-6 reported that 32.1% were receiving antimicrobials and provided details about the drugs used but not about the doses, routes of administration or indications. [286] In Sweden, Swedish strategic programme for rational use of antimicrobial agents and surveillance of resistance (STRAMA) established a method for national Point Prevalence Surveys of antibacterial use with web-based reporting. [161] STRAMA have co-ordinated three national point prevalence surveys of hospital antibacterial use in 2003, 2004 and 2006.[287] In addition, regional benchmarking studies have been conducted in Sweden with web based reporting systems.[118]

As described in ESAC introductory Chapter, the ESAC-1 project found measurement methods and therefore accuracy varied widely, limiting the conclusions of previous European-wide studies, and of ESAC-1 itself.[251] In the second phase of the ESAC project from 2004 to 2007, a hospital subproject was established to collect more detailed information from individual hospitals. The study aimed to collect data from hospital pharmacies for longitudinal analysis of antibacterial consumption and to establish the first European Point Prevalence Survey. The STRAMA web based data collection form was selected because it included key information about drug doses and routes of administration for prophylaxis and treatment in children and adults that would facilitate interpretation of data about antibacterial consumption.

7.3 Aims

To standardise a method for Point Prevalence Survey of antibacterial use in European hospitals from different healthcare systems, based on the STRAMA data collection and reporting method.

To collect, and make publicly available, data about prescribed daily doses (PDD) of antibacterials in hospital practice for comparison with WHO DDDs to inform the interpretation of data about antibacterial use from hospital pharmacies.

To identify targets for quality improvement.

7.4 Methods

ESAC national representatives were invited to participate in the study and to recruit one hospital to perform a Point Prevalence Survey of all inpatients on a single day. The 20 countries that took part were Austria, Belgium, Croatia, Czech Republic, Denmark, England, Estonia, Finland, France, Greece, Latvia, Lithuania, Malta, Netherlands, Northern Ireland, Norway, Poland, Scotland, Slovenia and Sweden.

Neotide®, the Finnish company that maintains the software for the STRAMA, produced an English language version. The software was customised for each hospital in that forms were based on their specialties and drug list. All hospitals collected data by case note review. A preliminary workshop was held during the ESAC annual meeting in September 2005 to agree the main components of the survey and to adopt the modified STRAMA form for a Europe-wide Point Prevalence Survey. A workshop for training on the methods for the Point Prevalence Survey and use of the web based software was organised in January 2006 in Prague. The training meeting reviewed pilot data from each of the participating hospitals and also used specimen cases from one hospital for

training in data entry in order to ensure consistency of interpretations of the indications for antibiotic use.

Hospitals sent their antibacterial and department lists to the central team in Dundee to aggregate them according to the STRAMA protocol for generic drug names and standard department lists. Although it was possible for STRAMA to adapt the lists there could be no change to the PPS protocol and therefore, STRAMA protocol for data collection in for Swedish hospitals was used. Another open workshop was held to test the final version of the ESAC-STRAMA during an ECCMID (*European Congress of Clinical Microbiology and Infectious Disease*) meeting in April 2007.

The survey was completed during two calendar weeks between 1st April and 31st May 2006. Surgical wards were surveyed on Tuesday, Wednesday or Thursday in order to capture information about prophylaxis in the previous 24 hours. Medical wards were surveyed on Monday, Tuesday, Wednesday or Thursday. Depending on the number of beds, the hospitals could decide to complete the survey over one or more days. However, the protocol specified that all beds in each administrative unit (e.g. Internal Medicine, General Surgery) should be completed in a single day.

Hospitals were asked to identify survey staff familiar with reading patient notes (e.g. infectious diseases specialists, microbiologists, pharmacists, infection control nurses). Hospitals could decide whether to have the survey completed by a single person or a team of people with relevant expertise.

All patients who were in the hospital at 8.00 a.m. on the days of the survey were included in the study. Patients who were receiving antibacterials at 8.00 a.m. on the day of the survey were identified and the details of the prophylaxis or therapy recorded on the data sheet. For surgical patients, administration of prophylactic antibacterials was

recorded in the previous 24 hours. The reason for this was to code the duration of prophylaxis as either one dose, one day or >1 day.

ESAC- PPS data collection form and a screenshot of STRAMA web-based patient registry are presented in Appendices A.7.1 and A7.2.

The diagnosis and indication for prophylaxis or treatment used the same diagnosis group, which was anatomically related to an organ or system. In addition to looking at all patient records, staff could request additional information from nurses, pharmacists or doctors. However, there was no discussion about the appropriateness of prescribing because previous studies have shown very poor inter-rater reliability for measurement even after training.[288] [152] Hospitals were given an option to assess whether the antibiotic prescribed was consistent with their local antibiotic policy.

The World Health Organisation's Anatomical Therapeutic Chemical (ATC) Classification of medicines was used to code antibacterials used.[265, 266] All systemic antibacterials in J01, and selected drugs from J04AB (only Rifampicin), A07AA (only oral Vancomycin and Colistin) and P01AB (only oral Metronidazole) classes were included. Actual prescribed doses were recorded both for adults and children for single and combination antibacterials (e.g. 960mg of Co-trimoxazole). Antibacterials are either presented by group (e.g. Cephalosporins) or by individual chemical substance (e.g. Cefazoline). Where necessary, the route of administration has also been specified. The survey form and a print screen of the STRAMA data entry page are provided in Appendices 7.1 and 7.2.

No personal patient data were collected and each patient was given a number during data collection and the same number was used during data entry therefore, approval of ethical committee was not considered for this survey.

This chapter presents key results. More comprehensive descriptive findings can be found in Appendix A.7.3

7.4.1 Statistical analysis

The 95% confidence intervals for the proportion of patients who received antibacterials in any hospital and for the ratio between prescribed daily doses and WHO Defined Daily Doses were calculated.[289] The ratio of PDD to DDD was used to compare two measures for each of the antibacterials. These ratios were also used to compare differences between PDD and DDD for different antibacterials. Hospitals were ranked by the percentage of patients who received antibacterials, and 95% confidence intervals (CI) for the ranks[290] calculated using Monte Carlo simulation for repeated sampling from the normal distribution around the observed value for each hospital.[291] Ten thousand simulations were performed in the calculation of 95% confidence interval of the rank. STATA version 9.2 was used for Monte Carlo simulations.

7.4.2 Data validity

STRAMA provided an online reporting system for most of the measures. However, there were some inconsistencies, for example due to hospitals using drug trade names in different languages, and in some entered doses with implausible values. The whole database was therefore downloaded for cleaning and validation (including contacting hospitals to check inconsistencies and potential errors). The analysis presented here is based on the cleaned and validated database. Published paper was performed directly on to the downloaded database.

7.5 Results

The twenty participating hospitals had a total of 15,593 beds (mean 778, median 672, range 247 to 2,459); fifteen were teaching hospitals with 14,360 beds (92% of the total)

and ten were tertiary care hospitals with 10,422 beds (67% of the total). All hospitals had at least one Intensive Care Unit (ICU), sixteen had paediatric units and nine had a paediatric ICU. Two hospitals (number 5 and 17) were infectious disease hospitals with 747 beds and ten of the remaining hospitals had Infectious Diseases departments. Haematology and renal dialysis units were present in twelve hospitals and nine hospitals performed organ transplantation.

On the day of the survey there were 11,571 patients in the 20 participating hospitals, of whom 3,483 (30.1%) were receiving antibacterials. Of the treated patients 1,653 (47.5%) were female and 371 (10.7%) were children <17 years old, of whom 145 (39%) were <5 years old.

The proportion of patients receiving antibacterials ranged from 19% to 59% (Figure 7.1a), with relatively narrow 95% CI for these proportions. On the face of it, this implies that it is relatively easy to distinguish hospitals with high and low proportions of patients treated with antibacterials. However, the 95% CI for the *rank* for each hospital show much greater uncertainty than the 95% CI for the proportion of patients receiving antibacterials (Figure 7.1b). For 12 of the hospitals the 95% CI for their rank crosses the median (10th) position so it is not possible to say with confidence that they are in the upper or lower half of the distribution for antibacterial use. However we can be 95% confident that four hospitals (5, 17, 2 and 20) are in the top 50% of antibacterial use and four hospitals (15, 9, 19 and 16) are in the bottom half.

Figure 7.1a: Percentage of patients treated with antibacterials with 95% CI (vertical bars) for 20 hospitals in the ESAC Point Prevalence Survey

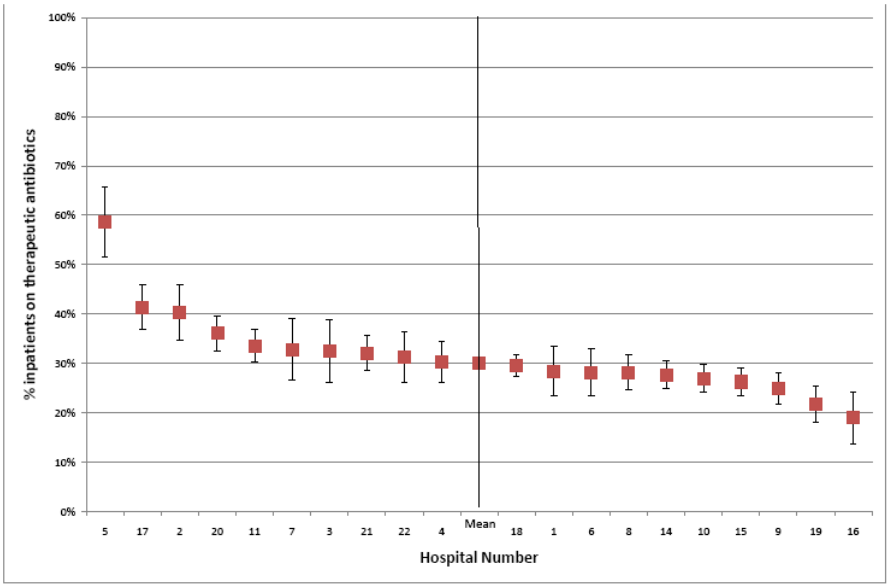
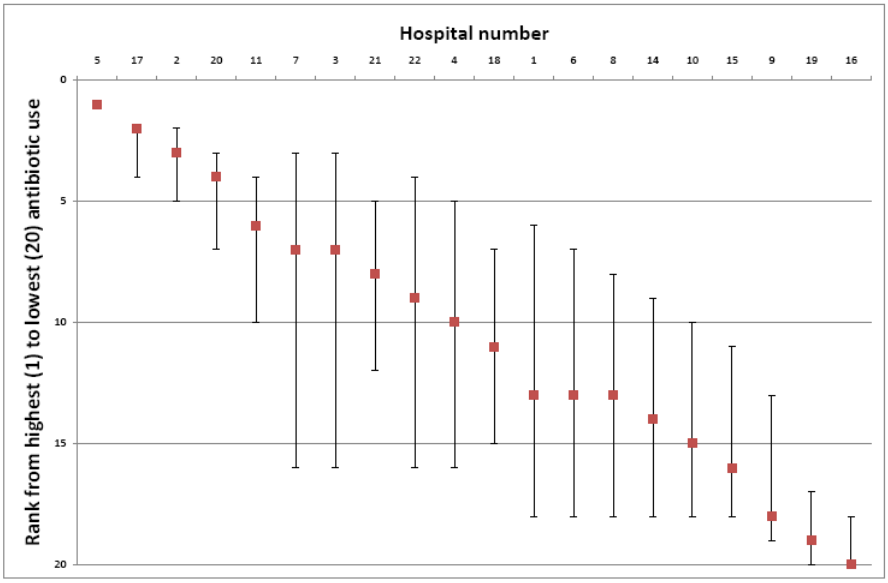


Figure 7.1.b: Estimated true ranks from 1 (highest) to 20 (lowest) users of antibacterials with 95% CI for ranks for the 20 hospitals in Figure 1a.



Treated patients received a total of 4,748 antibacterials. The indications were community acquired infection in 48.4% (n=2,299), hospital acquired infection in 30% (n=1,425), surgical prophylaxis in 15% (n=707), and medical prophylaxis in 6.7% (n=317). Examples of medical prophylaxis included long term prevention of recurrent urinary tract infection and prophylaxis in patients who were immunocompromised.

Samples for bacterial culture were obtained before therapy for a similar proportion of adults (43.0%, 1,822/4,242) and children (54%, 275/506). There was information about the indication for treatment in the case notes for 3,056 (64.4%) antibacterials.

The commonest anatomical systems identified as the site of infection were the respiratory tract (28.9%) for treatment, and intra-abdominal (22.9%) for prophylaxis (Table 7.1). The anatomical system was undefined for 569 (15.8%) antibacterials. Of these 275 (48%) were prescribed for sepsis with no defined site of origin, 168 (30%) for bacteraemia with no defined site of origin, and 126 (22%) antibacterials were prescribed to patients with completely undefined site of infection and with no systemic inflammation.

The antibacterials used for community acquired pneumonia were mainly broad spectrum: quinolones accounted for 11.2% and third generation cephalosporins 10.3% of therapies, whereas beta-lactamase sensitive penicillins only accounted for 3% of therapies (Table 7.2).

Table 7.1: Anatomical sites recorded for treatment and prophylaxis. The total (3,599) is greater than the number of patients treated (3, 483) because some patients had antibacterials prescribed for more than one anatomic site.

System	Site of infection	%	Prophylaxis	% of prophylactic use	Treatment	% of treatment use
Respiratory	867	24.1%	69	8.2%	798	28.9%
Skin, Bone & Joint	650	18.1%	131	15.6%	519	18.8%
Undefined	569	15.8%	103	12.3%	466	16.9%
Intra-abdominal	540	15.0%	192	22.9%	348	12.6%
Urinary tract	471	13.1%	99	11.8%	372	13.5%
Otorhinolaryngology	163	4.5%	113	13.5%	50	1.8%
Genital	133	3.7%	78	9.3%	55	2.0%
Cardiovascular	108	3.0%	29	3.5%	79	2.9%
CNS	86	2.4%	21	2.5%	65	2.4%
Eye	12	0.3%	4	0.5%	8	0.3%
Total	3599		839		2760	

Table 7.2: Antibacterials for community acquired pneumonia (n=580 antibacterials for 428 patients)

Antibacterial group	Number	%
Penicillins with betalactamase inhibitor	139	24.0%
Macrolides	88	15.2%
Fluoroquinolones	65	11.2%
Third generation cephalosporins	60	10.3%
Broad spectrum penicillins	56	9.7%
Second generation cephalosporins	56	9.7%
Other aminoglycosides	22	3.8%
Penicillinase sensitive penicillins	17	2.9%
Imidazol derivatives	13	2.2%
Lincosamides	12	2.1%
Carbapenems	10	1.7%
Tetracyclines	9	1.6%
Co-trimoxazole	7	1.2%
Glycopeptides	6	1.0%
Beta-lactamase resistant penicillins	5	0.9%
Nitroimidazol derivatives (oral Metronidazole)	5	0.9%
First generation cephalosporins	4	0.7%
Fourth generation cephalosporins	3	0.5%
Antituberculosis drugs (only rifampicin)	3	0.5%
Sum	580	

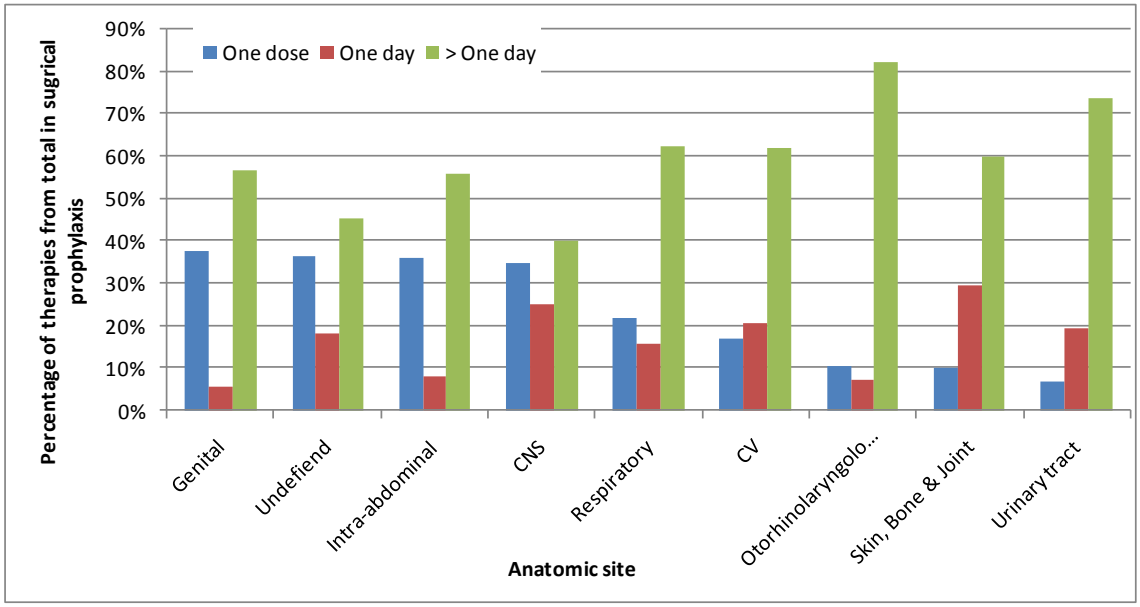
Duration of surgical prophylaxis

In surgical departments 511 patients received 616 therapies for surgical prophylaxis. The duration of antibacterial prophylaxes for surgery were one dose in 26% (155/602), and one day in 16 % (99/602). The duration of antibacterial prophylaxis for surgery was >1 day in 57.3% (384/602) of all patients who received prophylaxis, ranging from 42.9% for paediatrics to 90.0% for otorhinolaryngology (Table 7.3, Figure 7.2). Single dose pre-operative prophylaxis was used in 25.2% of patients, ranging from 6.7% for otorhinolaryngology to 45.1% for gynaecology (Table 7.3, Figure 7.2).

Table 7.3: Duration of surgical prophylaxis for patients in surgical departments

Department	Number of patients				% of total for Department			% of total for duration		
	One dose	One day	> 24h	Total	One dose	One day	> 24h	One dose	One day	> 24h
General Surgery	66	36	137	244	27.0%	14.8%	56.1%	51.2%	42.9%	46.8%
Orthopaedics	14	32	43	89	15.7%	36.0%	48.3%	10.9%	38.1%	14.7%
Gynaecology	32	5	34	71	45.1%	7.0%	47.9%	24.8%	6.0%	11.6%
Urology	7	6	43	56	12.5%	10.7%	76.8%	5.4%	7.1%	14.7%
Otorhinolaryngology	2	1	27	30	6.7%	3.3%	90.0%	1.6%	1.2%	9.2%
Paediatrics	8	4	9	21	38.1%	19.0%	42.9%	6.2%	4.8%	3.1%
Total, all departments	129	84	293	511	25.2%	16.4%	57.3%	100%	100%	100%

Figure 7.2: Duration of surgical prophylaxis by anatomic site presented as percentage antibacterial therapy per duration from total antibacterials used for surgical prophylaxis.



Comparison between average PDD and WHO DDD in adult patients

For adult patients, a WHO DDD was available for 59 parenteral antibacterials and 47 oral antibacterials that were used in the Point Prevalence Survey (Tables 7.4 and 7.5).[292] There was no difference in reported PDDs and WHO DDDs for 5 (10.6%) oral antibacterials and 11(18.6) parenteral antibacterials. The PDD exceeded the WHO DDD for 21 (44.7) oral antibacterials and 30 (50.9%) parenteral antibacterials. The PDD was less than WHO DDD for 21 (44.7%) oral antibacterials and 18 (30.5%) parenteral antibacterials. In order to identify variables that might explain the relationship between PDD and WHO DDD, in this study the preliminary focus was on the ten most commonly prescribed antibacterials for adults. In descending order these were: oral Ciprofloxacin (n=328), parenteral Cefuroxime (n=307), oral Amoxicillin plus enzyme inhibitor (n=285) parenteral Metronidazole (n=264), parenteral Amoxicillin plus

enzyme inhibitor (n=253), parenteral Ciprofloxacin (n=198), Piperacillin plus enzyme inhibitor (n=160), Cefazolin (n=157), Ceftriaxone (n=139), Gentamicin (n=104) (Tables 7.4 and 7.5). It was not possible to analyse the relationship between PDD and WHO DDD by hospital because the range of use of all 10 drugs was from 22 to 291 therapies per hospital and not one of the 10 drugs was recorded in every single hospital. Therefore, the relationship between PDD and WHO DDD for the top three indications: respiratory, intra-abdominal and skin or soft tissue infections (Figure 7.3) were analysed. We have only included eight drugs because there were less than 10 treatments for respiratory infections with Cefazolin or gentamicin. The data do not show any consistent relationship between indication and the ratio between PDD and WHO DDD. The 95% CI overlap for all drugs, suggesting that any differences are likely to be due to chance variation (Figure 7.3). Although there are only two oral antibacterials represented the data clearly show that the relationship between PDD and WHO DDD is formulation dependent. However, divergence may be different based on route of administration (for Amoxicillin plus enzyme inhibitors, the PDD to DDD ratio is higher for the oral formulation whereas the opposite applies to Ciprofloxacin).

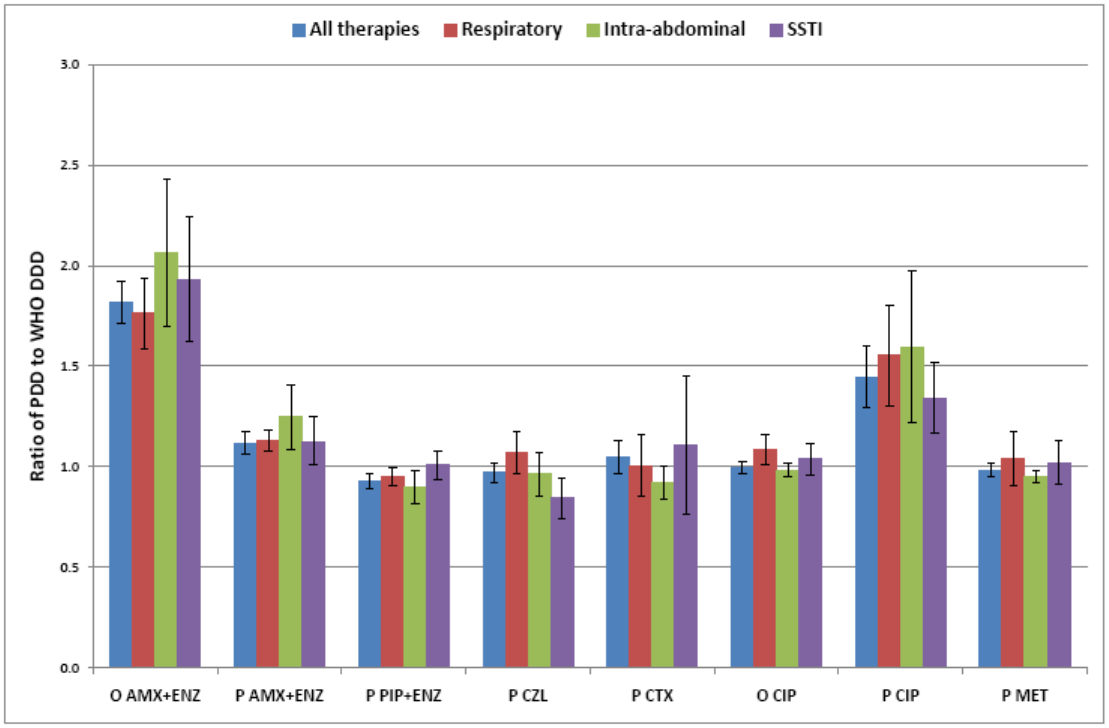
Table 7.4: Average Ratio of PDD (prescribed Daily Dose) to WHO DDD (Defined Daily Dose) for oral antibacterials prescribed more than 10 times for adults with corresponding confidence intervals (CI)

	Substance	Count	Average PDD/DDD	CI
1	Ciprofloxacin	328	0.99	0.47- 1.52
2	Amoxicillin and enzyme inhibitor	285	1.82	0.06-3.58
3	Sulfamethoxazole and trimethoprim	108	0.72	-0.43-1.87
4	Metronidazole	105	0.61	0.43- 0.80
5	Amoxicillin	103	1.71	0.05- 3.37
6	Clarithromycin	79	1.74	0.80- 2.68
7	Clindamycin	50	1.06	0.28- 1.84
8	Doxycycline	44	1.67	0.30- 3.04
9	Flucloxacillin	37	1.92	-0.97- 4.80
10	Cefuroxime	35	1.70	0.69- 2.71
11	Norfloxacin	29	0.97	0.60- 1.33
12	Cefalexin	28	0.84	0.08- 1.61
13	Ofloxacin	28	0.93	0.58- 1.28
14	Trimethoprim	28	0.95	0.56- 1.33
15	Phenoxymethylpenicillin	27	1.03	-0.34- 2.40
16	Erythromycin	26	1.25	0.24- 2.27
17	Moxifloxacin	23	1.22	-0.45- 2.88
18	Rifampicin	22	1.31	0.10- 2.52
19	Nitrofurantoin	20	0.87	-0.04- 1.77
20	Vancomycin	13	0.25	0.12- 0.38
21	Fusidic acid	11	0.94	0.55- 1.33
22	Pivmecillinam	11	1.00	0.23- 1.77
23	Dicloxacillin	10	1.33	0.37- 2.28
24	Azithromycin	10	1.60	-0.84- 4.03

Table 7.5: Average Ratio of PDD (prescribed Daily Dose) to WHO DDD (Defined Daily Dose) for parenteral antibacterials prescribed more than 10 times for adults with corresponding confidence intervals (CI).

	Substance	Average	Count	CI
1	Cefuroxime	0.97	307	0.14- 1.80
2	Metronidazole	0.98	264	0.42-1.55
3	Amoxicillin and enzyme inhibitor	1.12	253	0.23-2.00
4	Ciprofloxacin	1.45	198	-0.70-3.59
5	Piperacillin and enzyme inhibitor	0.93	160	0.50-1.36
6	Cefazoline	0.97	157	-0.09-2.03
7	Ceftriaxone	1.05	139	0.06-2.04
8	Vancomycin	0.80	131	0.02-1.58
9	Gentamicin	1.14	104	-0.90-3.17
10	Ampicillin and enzyme inhibitor	3.85	93	1.21-6.48
11	Benzylpenicillin	2.00	86	-0.52-4.52
12	Clindamycin	0.95	85	0.28-1.62
13	Imipenem and enzyme inhibitor	0.97	68	0.30-1.64
14	Cefotaxime	1.46	67	0.10-2.82
15	Ampicillin	2.43	57	0.37-4.49
16	Meropenem	1.55	55	0.11-2.98
17	Ceftazidime	1.09	50	0.28-1.90
18	Flucloxacillin	3.36	37	-3.88-0.60
19	Cloxacillin	3.26	35	0.37-6.14
20	Amikacin	0.96	33	0.36-1.56
21	Oxacillin	2.51	33	-0.06-5.08
22	Teicoplanin	1.16	30	-0.04-2.36
23	Cefoxitin	0.45	28	-0.06-0.95
24	Amoxicillin	4.39	26	-2.16-10.95
25	Ticarcillin and enzyme inhibitor	0.96	19	0.61-1.31
26	Levofloxacin	1.38	17	0.31-2.45
27	Cefipime	1.96	17	0.44-3.47
28	Spiramycin	0.72	12	-1.00-2.44
29	Netilmicin	0.79	11	-0.06-1.64
30	Sulfamethoxazole and trimethoprim	1.45	11	-1.76-4.67
31	Tobramycin	1.70	10	-0.30-3.70
32	Erythromycin	2.07	10	-0.56-4.69

Figure 7.3: Ratio of prescribed daily dose (PDD) to WHO Defined Daily Dose (DDD) for eight formulations of antibacterials that were prescribed to at least 10 adults for each of the three commonest indications for therapy.



Abbreviations: O AMX+ENZ: Oral Amoxicillin and Enzyme inhibitor. P AMX+ENZ: Parenteral Amoxicillin and Enzyme inhibitor. P PIP-ENZ: Parenteral Piperacillin and Enzyme inhibitor. P CZL: Cefazoline. P CFX: Parenteral Cefuroxime. O CIP: Oral Ciprofloxacin. P CIP: Parenteral Ciprofloxacin. P MET: Parenteral Metronidazole**.**

7.6 Discussion

This study showed that a web based method for collection of point prevalence survey data with automatic reporting could be implemented successfully in all 20 participating hospitals. The dataset that was analysed was limited than the original STRAMA dataset. Three measures in STRAMA protocol and PPS data collection forms (Appendix A.7.1), namely, assessment of the appropriateness of antibacterial therapy, information about implanted devices, and immunosuppression were not analysed. Assessment of appropriateness was highly dependent on existing a local policy and personal judgments and two latter measures were rarely recorded. However, a consistent method was established for collection of basic data about antibacterial use that will facilitate future cross-sectional and longitudinal comparison between hospitals and countries. However, hospitals and policy makers need to be aware that data collection and processing are too time consuming to make frequent international hospital wide surveys a sustainable solution to the problem of overuse of antibiotics.

Previously published studies show wide variation in the prevalence of antibiotic use, from 16.6% to 49.3% (Table 1.2, Chapter 1). However, this range of use is likely to be explained at least in part by the inconsistency of data collection with respect to the population of patients and the inclusion or exclusion of surgical prophylaxis (Table 1). It is striking that the STRAMA national surveys in Sweden in 2003 and 2004 reported almost identical prevalence (30.9% and 31.9%), which suggests that prevalence of use may remain stable over time.[293]

In this survey there was wide (three fold) variation in antibacterial consumption between European hospitals (Figure 7.1a). Nonetheless there was considerable variation in the ranking of hospitals and only 8 or the 20 hospitals could be reliably

placed in the top or bottom half of ranking by antibacterial use (Figure 7.1b). Ranking is a notoriously unreliable method for comparing the performance of hospitals.[294] The purpose of ranking was to assess the reliability of classifying hospitals as relatively high or low users of antibacterials as a precursor to understanding the hospital characteristics that may explain variation in antibacterial use. For example, two of the four hospitals with antibacterial use reliably in the top half of the distribution were specialist infectious diseases hospitals. Policy makers need to resist the temptation to rank hospitals by antibacterial use as a performance measure for two reasons. First most of the variation in ranking cannot be distinguished from chance. Second a significant proportion of systematic, non-chance variation in ranking is likely to be explained by differences in case mix.[295]

Three targets were identified for quality improvement. First, the duration of pre-operative prophylaxis was >24 hours for the majority of patients in all surgical specialities. While there is continuing debate about the effectiveness of single dose prophylaxis *versus* additional post-operative doses, [296] there is no evidence to support prolonging surgical prophylaxis for more than 24 hours.[297] The target for prophylaxis >24 hours should therefore be 0% for all specialties. [298] Second, the range of antibacterials used to treat pneumonia was not consistent with evidence based guidelines that are in place in most European countries.[299] In particular the use of penicillinase sensitive Penicillins was very low (Table 7.2). Third, the documentation of antibacterial therapy is still poor. Although the average for documentation of indication (64.4%) was higher than in previous audits [300] it is still unacceptably low. Documentation should be the rule, meaning that >95% recording should be expected.[298]

The WHO DDD is the single most commonly prescribed daily dose worldwide. Because the use of antibiotics is much commoner in ambulatory care than in hospitals it

is expected that doses in ambulatory care would be lower than in hospitals so that the WHO DDD would be consistently lower than PDD, especially for oral drugs. However, this study showed that the WHO DDD was almost as likely to be greater than PDD for oral and parenteral medicines. Shifts between drugs could result in substantial change in DDDs used at hospital level that is purely due to changes in the drugs prescribed, not the number of patients treated. For example a shift in antibiotic policy from parenteral Ciprofloxacin to parenteral Amoxicillin plus enzyme inhibitor would result in a 50% fall in DDD even if the same number of patients were treated for the same number of days (Figure 7.3). Consequently, differences between hospitals in antibacterial use measured in DDDs are explained at least in part by differences in the choice of drugs that are used, in addition to differences in the number of patients treated or the duration of therapy. These results add to the evidence from ESAC ambulatory care studies, which suggests that the WHO DDD should not be used as the sole measure of antimicrobial use.[301]

7.7 Conclusion

In conclusion, the strengths of this study are that web based PPS methodology can be applied successfully to surveillance of antibacterial prescribing in hospitals from 20 different countries and that the results identify targets for quality improvement. In providing a range of analysis for anatomic sites together with indications and most commonly used antibacterials, this chapter could provide an insight into hospital antibiotic use and highlight the areas that require further investigation. The study could introduce a feasible standardised, reproducible, simple, and cost-effective system that can be used as a tool to improve quality of care in hospitals at regional, national, local, and hospital level. The results could help countries develop cost-effective public health strategies and to inform best practises of management for individual patients. It could

provide a tool that will allow recording of indicators and setting of targets for audit purposes which can be utilised to improve management of the individual patient, monitoring of antimicrobial policy, and to reduce antimicrobial selective pressure on hospital micro-organisms.

The weaknesses of the study are that only included one hospital per country was recruited and the hospitals were very heterogeneous in size and specialty mix. The method will require further testing with more hospitals in order to fully assess generalisabilty. In 2006, the ESAC team made a successful bid to the European Centre for Disease Control (ECDC) to continue funding the project. This bid included the method for Point Prevalence Survey that tested in this study.[302] ESAC has developed and tested an online database in 52 hospitals in 2008 with the aim of conducting a much larger survey in 2009 in order to investigate hospital characteristics that explain variation in antibacterial use. This study also added the value of a new collaboration with the World Health Organisation for point prevalence surveys on use of antimicrobials in children in the ARPEC project (Antimicrobial Resistance and Prescribing in European Children.[303]

CHAPTER EIGHT: THE EUROPEAN SURVEILLANCE OF ANTIMICROBIAL CONSUMPTION (ESAC) – HOSPITAL CHARACTERISTICS

8.1 Background

Quality indicators measure various aspects of the quality of care provided. They can apply to structures, processes or outcomes of care.[304] Structural indicators focus on organisational aspects of care provision, such as the availability of specific clinics, appointment systems or equipment. Longitudinal and Point Prevalence Surveys were the two main components of the ESAC-2 Hospital Care project (Chapters 5, 6 and 7). A questionnaire about a country's health-care system and hospital demographics was designed to identify potential explanatory variables in future comparisons between countries or hospitals. In this chapter the characteristics of the hospitals that participated in the ESAC-2 HC Subproject are described. The study used a mixed, partially close-ended and open-ended questionnaire to collect data about case-mix and organisational factors that might explain variation in longitudinal and cross sectional measures of antibiotic use.

8.2 Aims

To identify structural characteristics of European hospitals that might explain variation in the use of antibiotics.

8.3 Introduction

Different determinants at different levels, such as cultural, organisational and behavioural factors, might influence hospital antibiotic prescribing and cause antibiotic use to vary in different hospitals. Understanding these hospital characteristics at regional, national, and international level can lead to improvements as these

determinants can provide a base on which to build strategies to enable more appropriate use of hospital antibiotics.

As early as the 1970s it was recognised that to achieve effective control of hospital antibiotic use a combined approach from all levels and disciplines within and across the organisations was required.[305-307] Establishment of a multi-disciplinary committee for antibiotic management as a separate team or as a part of a drugs and therapeutic committee helped organisations to promote their antibiotic prescribing activity. Key functions of antibiotic committees that were identified in these early studies included development of local formulary and guidelines, evaluation of antibiotic use through regular audits, providing feedback to physicians, identifying areas requiring further study by hospital ward or by disease or antibiotic and education of students or staff.[305-307] Recent studies have emphasised the importance of integrating hospital infection control committees and hospital antibiotic management committees, with hospital therapeutics committees and pharmacy and microbiology departments are important steps toward improving antimicrobial use and reducing collateral damage from antibiotics in secondary care.[19, 238, 276, 308-311] Nonetheless, despite over forty years of accumulated evidence about the benefits of antibiotic policies not all of hospitals adhere to elements of effective leadership in antibiotic prescribing. The ARPAC study found that only 57% of 170 European hospitals had antibiotic policies.[312]

Avorn stated that in teaching hospitals, prescribing decisions are frequently made by those with the least clinical experience (interns and residents) and, at the same time, each year hospitalised patients become more acutely ill and their cases increasingly complex. These factors, combined with the continuous pressure of keeping length of hospital stays short, make it difficult to pursue a course of watchful waiting in managing a fever of unknown origin. [313] Such control is particularly difficult if the prescribing

physician has been in practice for only a few months. The first priority becomes the prevention of disaster within the next 24 hours, a goal often thought to be met best by broad-spectrum antibiotics or a combination of narrower-spectrum agents used in combination.[313] In a study of 145 hospitals across Germany university affiliation was associated with a comparatively high use of antibacterials measured in DDD/ patient-day in the whole hospital, in the ICU and Haematology wards. The authors suggested that in comparative analyses of hospital antibiotic consumption, data needed to be adjusted at least for university affiliation and haematology-oncology units.[283] Nonetheless, in 13 Norwegian hospitals despite variations in total use, the type of hospital did not have any association with total antibacterial use but type of therapeutic choice of antibacterial agents differed and university hospitals used more 3rd generation Cephalosporins. [314] In a multicentre study in 83 French hospitals being a public teaching hospital (OR= 10, P value=0.02) and having non-acute care beds less than or equal to 25% (OR=5.6, P value 0.03) were associated with higher antibiotic use. However, use of a nominative delivery form to record individual patient use of antibiotics was associated with significantly lower total use (OR= 0.3, P=0.04). Other factors had no significant effect. [315] These studies suggest that hospital type affects antibiotic use and makes it more complex, however, this factor acts in different ways in different regions or countries.

Antibiotic use in Intensive Care Units and Haematology units was much higher than medical and surgical wards in groups of hospitals in France and Germany.[315, 316] In 47 teaching hospitals in the US while all hospitals had antibiotic policies, teaching hospitals were significantly more likely than other hospitals to have clinical practice guidelines for the treatment of community acquired pneumonia (OR, 4.2; CI95, 1.03-17.4) or the use of Vancomycin (OR, 3.8; CI95, 1.03-14.3). In the same study, hospitals

that routinely used either informal or formal pharmacy consultations for initial antimicrobial choice were less likely to have restriction policies (OR, 0.24; CI95, 0.07-0.88). However, a similar association was not found between hospitals reporting the routine use of infectious disease (ID) consultations to influence initial antimicrobial selection and having restriction policies (OR, 0.87; CI95, 0.24-3.12). [317]

Patients on maintenance haemodialysis are at a high risk of infection because of the prolonged need for vascular access, particularly in haemodialysis centres where many patients are receiving dialysis concurrently. In this setting there are repeated opportunities for person-to-person transmission of pathogens, directly or indirectly, via contaminated devices, equipment and supplies, environmental surfaces, or the hands of health care workers. These patients are at high risk of being colonised with antimicrobial-resistant bacteria like MRSA, VRE, Vancomycin-resistant enterococci, and multidrug-resistant gram-negative bacteria. The use of antimicrobials in renal dialysis patients is much higher than in other patients.[318, 319] In other hospital wards like haematology and organ transplant, patients are immunodeficient and receive multiple antibiotics for prophylaxis therefore, the use of antibiotics in hospitals with these specialities may be higher.

A multicentre survey included 2,000 patients with Community Acquired Pneumonia (CAP) treated at 5 different outpatient sites in 3 different regions of Canada. The patients were prescribed a total of 23 different antibiotic regimens. Significant variations in prescribing rates occurred for 17 of these antibiotics regimens across the different sites.[320] Such variation suggests that local factors, such as formulary restrictions and opinion leaders, have a strong impact on actual patterns of antibiotic prescribing. On the other hand, there is little evidence to suggest that national guidelines have much impact on individual antibiotic prescribing decisions. In the same

study, only 46% of outpatients were prescribed antibiotics consistent with the American Thoracic Society guidelines.[321, 322] For a cross-sectional questionnaire study about antibiotic treatment choice for CAP in the US, a sample of 400 generalist physicians and 429 infectious diseases specialists were selected. The authors found that both generalists and ID specialists were more likely to prefer newer and broad spectrum antibiotics compared with older agents recommended by national guidelines. The majority (64%) of infectious disease specialists disagreed with the statement that new drug development would keep pace with the problem of antibiotic resistance compared with 49% of generalists, yet the infectious diseases physicians had much stronger preferences for using newer drugs (e.g. Azithromycin rather than Erythromycin).[322]

A study to assess the knowledge of junior doctors found that only 48 and 67%, respectively, could define severe sepsis and shock correctly. Only 40% used the local sepsis protocol and 26.7% used microbiology or ID physician advice. From the total, 65% did not recognise that parenteral antimicrobials were significantly (10-fold) more expensive than oral antimicrobials which may contribute to excessive use of parenteral use and a late switching from parenteral to oral antibiotic therapy. [323] Another survey investigating the knowledge and attitudes of junior doctors about microbial resistance and antibiotic prescribing in 2 teaching hospitals in Scotland and France with different cultural contexts revealed that collectively from 139 participants, only 63% believed that resistance was a problem in their clinical practice and the perception that resistance was a problem was not influenced by their past training experience. Trainees in two centres seemed to behave differently in seeking advice from senior colleagues, microbiologists and pharmacists in their prescribing decision. [324] Hospital antibiotic use is a multidisciplinary decision in conjunction with medical microbiologists, junior doctors, pharmacists and infection control nurses. Nonetheless in a systematic review

of interventions to improve hospital antibiotic use only 17% of 66 eligible studies used multidisciplinary teams.[148] Nosocomial infections are associated with low nurse/patient ratios. [325] Infection control nurses lead interventions like reducing the unnecessary use of urinary catheterisation in urinary tract infections [326] and campaign to target hand hygiene[327] besides contributing to control measures such as barrier precautions hand washing, gloving, gowning, and isolation.

The aim of this study was to document the availability of data that might explain variation in use of antibiotics by hospitals and to analyse the relationship between these data and two measures of hospital antibiotic use: point prevalence and total use in the previous year. The literature reviewed suggested that five specialties are likely to have higher use of antibiotics: Haematology/Oncology, Infectious Diseases, Intensive Care, Renal Dialysis and Organ Transplant. Consequently beds were grouped from these five specialties and assessed the relationship between antibiotic use and the high user beds as a % of total.

8.4 Methods

8.4.1 Design of the hospital questionnaire

A first version of the hospital questionnaire was designed from published literature and practice based knowledge. It was then reviewed by 28 members of the ESAC-2 Hospital Care project. The team included ID consultants, microbiology consultants, ID pharmacists, epidemiologists, and ID nurses, all from the secondary care sector. During a workshop in January 2006 the questionnaire was developed and revised with reduction in the number of questions and clarification of key issues. The final version had 45 questions in five categories covering a 6-year period starting from year 2000 on a yearly basis. The questionnaire included both closed, quantitative questions and open ended descriptions. It included five groups of questions: 1) population and hospital

demographic characteristics, 2) economic factors, 3) information about pharmacy stock and dispensing; 4) microbiology related factors, 5) managerial factors (Appendix A.8.1).

Concerning population and hospital related factors, participants were asked for the following information: the estimated population coverage of the hospital, number of beds, hospital category (teaching versus non-teaching) secondary or tertiary versus general district hospital. The rest of the questions in the first block were about presence of specific specialities and the proportion of beds from the total. The specialties were: ICU, paediatrics ICU, Paediatrics, infectious disease, renal dialysis, haematology, organ transplant, and long term care like psychology. In the same block, hospitals were also asked about the number of pharmacists, ID physicians, microbiologists, and infection control nurses.

Concerning economic factors, hospitals were asked about source of drug expenditure nationally and within the hospital, contribution of patients to drug expenditure, and financial incentives related to antibiotic prescribing.

The third section had 10 questions about pharmacy stock and dispensing factors. They included those factors that might influence collection of data in the ESAC longitudinal survey, which were supposed to be only from inpatient destinations. Examples were antibiotic supply from sources other than hospital pharmacy, exclusion of wasted drugs, of drugs returned drugs to the hospital pharmacy and the ability to identify antibiotics prescribed for administration in the community (prescriptions on hospital discharge or from outpatient clinics. There were also questions about occasional antibiotic shortages, removal of antibiotics from supply lists, drug donations or changes in dispensing strategies over the last 6 years.

Concerning microbiology related factors, changes in policy and facilities in quality and the selection criteria of patients' specimens was considered.

The last group of questions included 13 questions on the presence of: Infection Control Committee (ICC) and Antibiotic Management Group (AMG), training medical students targeted at antibiotic prescribing, antibiotic guidelines in printed or electronic formats, online decision support systems against antibiotic prescribing as a routine basis, regular feedback on antibiotic use and resistance, interventions to improve antibiotic prescribing, and activities to improve antibiotic prescribing or infection control and hospital cleanness.

Each hospital was allocated the same number as in the ESAC longitudinal and point prevalence surveys.

8.4.2 Descriptive Analysis

For continuous variables, in addition to standard deviations, the coefficients of variation (CV) were calculated. In statistics, the CV is normalised and therefore a comparable measure of dispersion.

$$CV = \frac{Standard\ Deviation}{Mean}$$

The standard deviation of data must always be understood in the context of the mean of the data. The coefficient of variation is a dimensionless number. So when comparing between datasets with different units or widely different means, one should use the coefficient of variation for comparison instead of the standard deviation. A CV <1 (or <100%) is considered as small variation, CV>1(or <100%) shows big variations in the outcome and a CV around 3 (or 300%) suggests complete dispersion. The CV cannot be calculated when the mean of a variable is zero but this did not apply to any of the variables in this study.

8.4.3 Statistical analyses

Various recommendations exist for the minimum number of observations for a valid multiple regression. With N being the number of observations and *m* being the number of predictor variables, Green [328] suggested: $N \geq 50 + 8m$, where *m* is the number of predictor variables. Where assumptions are violated, greater sample sizes may be required.[328, 329] In this study, the number of hospitals was too small to conduct a multivariate regression for any independent variable obtained from the PPS or LS projects. Accordingly, simple regression was used to investigate the influence of each of the hospital characteristics on:

1) Proportion of patients receiving antibiotics / total admitted patients in PPS and

2) Total antibacterial use in year 2005 measured as DDD per number of beds.

The information drawn out of the questionnaire consisted of continuous and categorical variables. Correlations between the variables were examined, however the number of observations limited the method and number of variables that could be included. The Phi (Φ) test is the same as Pearson correlation, for two categorical variables which is also a function of the chi-square of fourfold table. Its improved versions are: Cramer's W and Cohen's W (the latter one for tables with more than 2 rows or columns). [330] The number of observations in each cell of a cross-tabulated table should not be less than 6. [331] In this study, all pairs of categorical cross-tabs had one or more cells with the number of observations less than 6. The other way of finding correlation between categorical variables was logistic regression. Logistic regression uses a maximum likelihood to get the estimates of the coefficients. According to Long, 100 is a minimum sample size, and at least 10 observations per predictor are needed. [332] Accordingly, for this study the pairs of categorical characteristics could not be tested for autocorrelations.

Pairwise correlations among variables of hospital characteristics were tested for those pairs where at least one was a continuous variable.

STATA version 9.2 was used for statistical analysis.

8.5 Results

The response rate was 90% (20 out of 22 hospitals). These hospitals also participated in:

- PPS and LS: 14 hospitals
- PPS and one year (2005) longitudinal data: 2 hospitals
- LS only: 2 hospitals
- PPS only: 2 hospitals.

The majority of the hospitals submitted their questionnaire with only one year, 2005, data. In total 34 questions were answered by nearly all hospitals from which 22 were categorical variables. These variables were coded as no (1), to some extent (2), and yes (3) in the statistical analysis.

8.5.1 Main characteristics

In 20 hospitals, the total number of beds was 15,845. 1,841 beds (12% from total) were in 5 (25%) non-teaching hospitals and (88%) were in 15 (75%) teaching hospitals.

There was 65% variation in hospital size which was less in non-teaching hospitals than teaching hospitals (39% versus 55%) (Table 8.1). The definition of secondary and tertiary hospitals varied in different European countries so the outcomes of being a secondary or tertiary hospital were combined. Only one hospital was a general district or primary care hospital. The other 19 hospitals were secondary or tertiary and the variation in the number of beds was 62%, a little less than the total for hospitals because the general district hospital was a relatively small hospital.

Table 8.1: Descriptive data and coefficient of variation test results for general hospital characteristics and number of special hospital beds

	Number of hospitals	Number of beds Total (Range)	Mean ± SD[ɛ]	CV[†]
Number of beds	20	15,845(243-2459)	793 ± 514	0.65
Teaching	15	14,360(247-2,459)	934 ± 517	0.55
Non teaching	5	1,841(243-593)	368 ± 144	0.39
General district	1	243		
Secondary or tertiary	19	15,611(247-2,459)	822 ± 511	0.62
Special Beds	Number of hospitals responded (with non-zero values)	Range in percentage from total beds		
ICU	19 (19)	0.93- 9.1	3.4±2.1	0.62
Paediatric ICU	14(9)	0-3.6	1.0±1.1	1.1
Paediatrics	19(16)	0-38.1	10.2±10.2	1.0
Infectious diseases	18(12)	0.0-100	7.2±23.2	3.2
Infectious diseases excluding hospital 5	17(11)	0.0-6.2	1.8±2.1	1.2
Haematology	17(13)	0.0-6.0	2.4±1.9	0.8
Renal dialysis	16(11)	0.0-4.3	1.4 ±1.4	1.0
Organ transplant	15(3)	0.0-6.4	0.6 ±1.7	3.0
Total special beds cause higher antibiotic use	19	1.34-106.1	14.9 ± 22.7	1.5

[ɛ]: Standard deviation. [†]: Coefficient of variation. Number of special beds was not available from hospital 19.

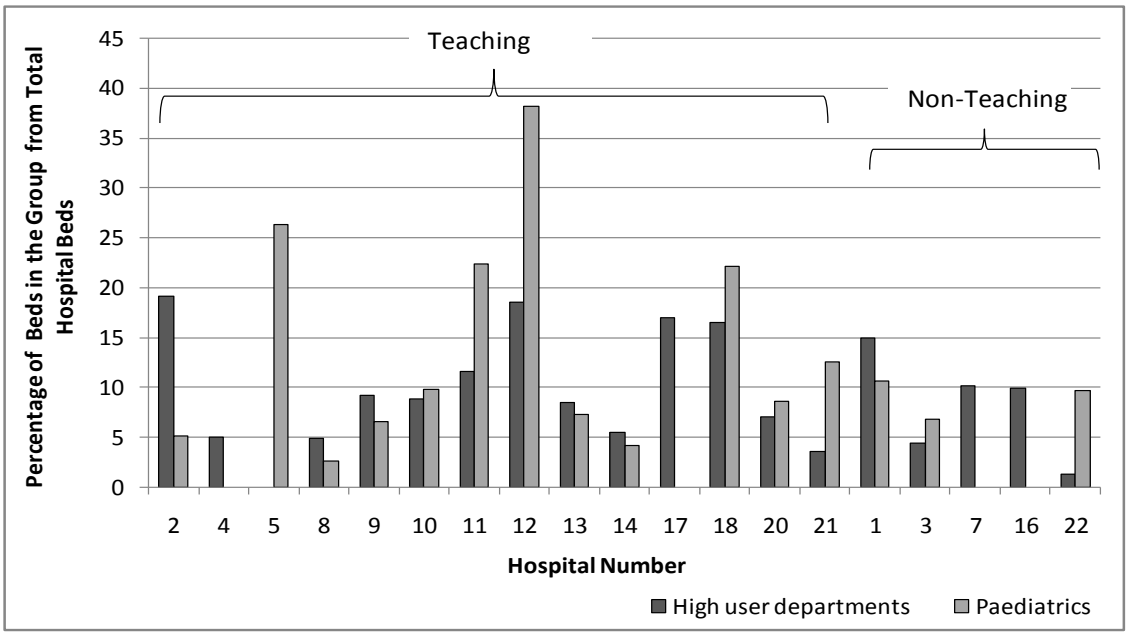
8.5.2 Special beds

The second part of Table 8.1 presents the number of special beds which are assumed to be associated with higher or lower antibacterial use than the average use in each hospital. The special beds do not necessarily correspond to the existence of a specific ward in all hospitals. In some hospitals the specialty existed but the number of

allocated beds was not fixed. All hospitals had ICU beds, except one. Sixteen hospitals (84%) had paediatrics. The frequency of having haematology, renal dialysis, and infectious disease beds were 68%, 58%, and 63%, respectively. Only 3 hospitals had organ transplant beds. Hospital 5, was an infectious disease (ID) hospital with 100% ID beds. Excluding this hospital changes the range of ID beds from 0-100% to 0-6.2%. Paediatrics beds had the second largest range 0-38.1% with 100% variation. The CV was lowest for ICU beds (62%), followed by haematology beds (80%). Variations for paediatrics ICU, ID beds (excluding one of the ID hospitals) and renal dialysis were 100 to120%. For organ transplant beds, the outcome (CV=300%) is completely dispersed. The total number of beds associated with higher antibiotic use ranged from 1.34% in hospital 22 to 106.1% in hospital 5 with a CV of 150% (Table 8.1).

Figure 8.1 shows, by hospital presentation, the total percentage of beds with high antibiotic use and paediatrics. The hospitals are grouped into teaching and non-teaching categories. Hospital 5 is excluded from the first group (high user beds) as an outlier from the graph. There was no information from hospital 19 in this set of questions. Hospitals 7, 16, and 17 had no paediatrics beds. Hospitals 2, 12, 17, 18, and 1 with more than 15% special beds were teaching hospitals except for hospital 1. Hospitals 12, 5, 11, and 18 with more than 15% paediatrics beds were all teaching hospitals. In teaching hospitals, the percentage of total special beds associated with a higher use of antibiotics and paediatrics was 16.8%±24.5%, CV=150% and 11.9% ± 11.3%, CV= 95%, respectively. In non-teaching hospitals, the average number of high user beds and paediatrics beds were 8.2%±5.4%, CV=66% and 5.4%±5.2%, CV =95%, respectively. In total the percentage of high user beds was 14.9%± 22.7%, CV= 153% and that of paediatric beds was 10.1% ± 10.3%, CV= 101%.

Figure 8.1: Percentage of total number of high antibiotic user beds from total hospital beds (including: ICU, infectious disease, haematology, renal dialysis, and organ transplant) and percentage of paediatrics beds, low user beds. No information was available from hospital 19. Hospital 5 with 100% ID beds is excluded from the first group.



8.5.3 Key specialities

The next part of the questionnaire was the percentage of full-time employee (FTE) of 4 clinical disciplines; ID physician, pharmacist, microbiologist, and infectious control nurse. Hospital 13 could not provide data for the number of pharmacists.

In 6 hospitals (4, 8,13,17,19, and 22), four of which were teaching hospitals, the number of ID physicians was zero (Table 8.2 and Figure 8.2). There were more than 300% variations in the number of ID physicians including hospital 5 with 21 ID physicians per 100 beds. However, excluding hospital 5, the variation reduces to 110%. Pharmacists were the largest group of clinicians (mean 1.5) and variations across the hospitals were 80%. The average number of pharmacists per 100 hospital beds in Europe was estimated to be 0.93. [333] Only nine (47%) of the hospitals had more than 0.93

pharmacists per 100 beds (hospitals: 20, 16, 21, 8, 7, 9, 14, 3, and 12), (Figure 8.2). It included 36% of teaching hospitals but 60% of non-teaching hospitals. The average number of pharmacists in teaching hospitals was 1.4 FTE/100 beds and 1.8 FTE/100 beds in non-teaching hospitals.

Figure 8.2: Total number of full-time employee (FTE) specialties. Hospital 5 was excluded. Hospital 13 could not provide information about number of pharmacists.

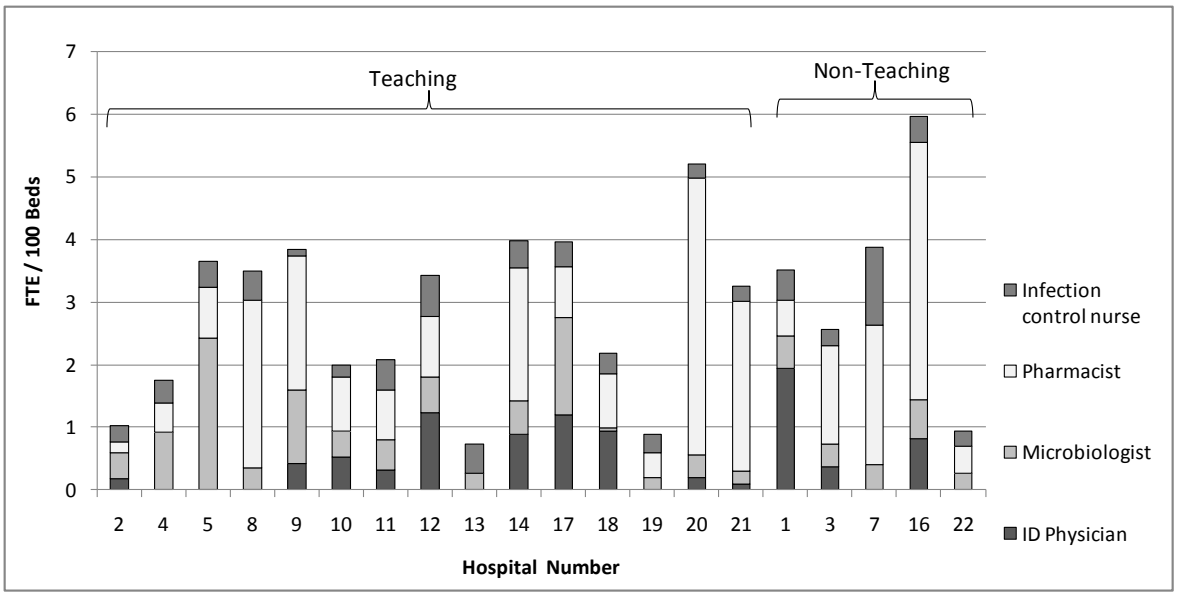


Table 8.2: Descriptive data and coefficient of variation test results for the number (%) of full time employee (FTE) specialties per 100 beds.

Discipline	Number of Hospitals[#]	Range	Mean ± SD*	CV[†]
ID Physicians	14(70%)	0.0-21.1	1.5 ± 4.6	3.1
ID physicians excluding	13(65%)	0.0-1.9	0.5 ± 0.6	1.1
Microbiologist	20(100%)	1.5-2.4	0.6 ± 0.6	1
Pharmacist	19 (100%)	0.2-4.4	1.5 ± 1.3	0.8
Infection control nurse	20(100%)	0.1-1.3	0.4 ± 0.2	0.6

[#]: Number of hospitals refers to hospitals with non-zero values. One hospital could not obtain data for number of pharmacists. *: Standard deviation. [†]: Coefficient of variation

The mean number of microbiologists in all hospitals was 0.6 FTE/100 beds with 100% variation (Table 8.2). The mean number of microbiologists in teaching hospitals was 0.66/100 beds and 0.44/100 beds in non-teaching hospitals. A greater number of microbiologists (>0.9/100beds) was present in four (20%) of the hospitals (numbers: 5, 17, 9 and 4). Hospitals 5 and 17 were ID hospitals (Figure 8.2). All hospitals had infection control nurses. The number of infectious control nurses was fewer than other clinicians (mean: 0.4/100 beds) ranging from 0.1/100 bed in hospital 12 to 1.3 in hospital 7 which was a non-teaching hospital. In two ID hospitals (5 and 17) the number of infection control nurses was close to the mean (Figure 8.2). Antibiotic management factors aggregated for all hospitals are presented in Figure 8.5.

8.5.4 Pharmacy stock data and pharmacy dispensing policies

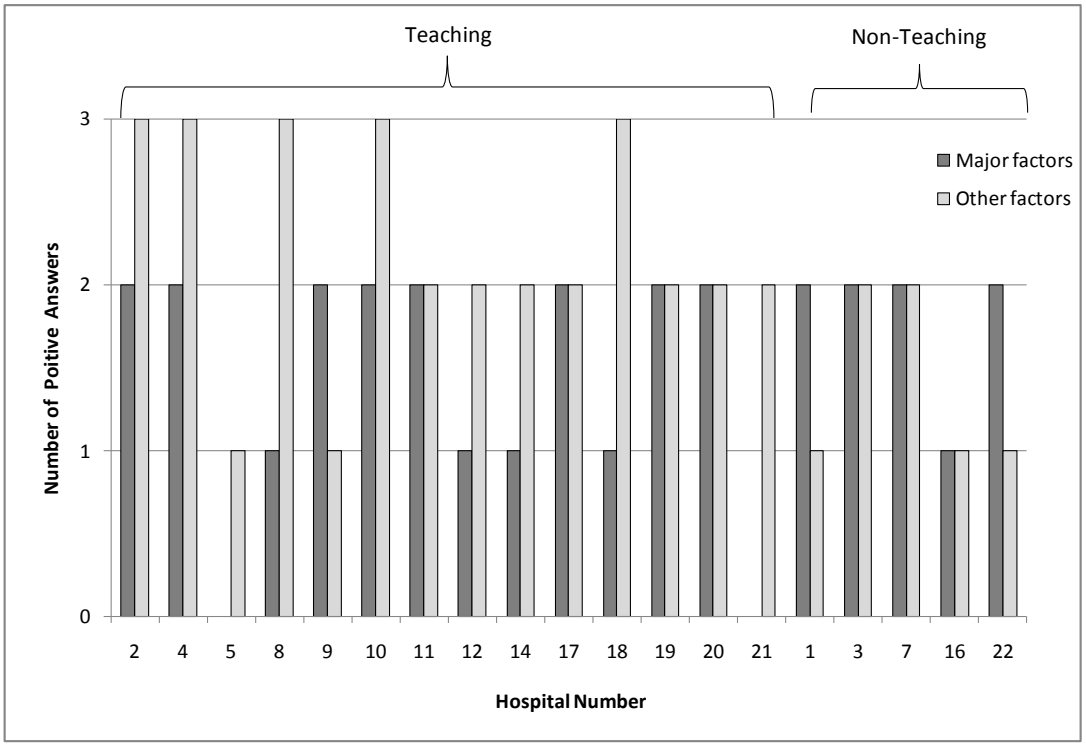
Data were available from 19 hospitals. One of the hospitals, hospital 13, could not get any information from its pharmacy department. In 17 hospitals (90%), all antibiotics were supplied only by pharmacy stock while in two other hospitals, the drugs sometimes might be provided from out of hospital sources. In 74 % (n=14) of hospitals, prescriptions at discharge were excluded from inpatient dispensing data. In 79 % (n=15) of outpatient clinics were excluded from in-patient destinations. In 53% (n=10) wasted drugs were deducted from pharmacy stock data and in 60 % (n=11) of hospitals returned drugs from hospital wards were deducted from pharmacy stock data (Table 8.3).

Table 8.3: Pharmacy dispensing characteristics.

	Number of hospitals (percentage from total number of hospitals)		
	Yes	No	To some extent
All antibiotics provided by hospital pharmacy	17(89.5)	1(5.3)	1 (5.3)
Prescriptions at discharge excluded	14(73.7)	4 (21.1)	1 (5.3)
Outpatient clinics excluded	15(79)	3(15.8)	1(5.3)
Wasted drugs deducted from data	10(52.6)	9(47.4)	0
Returned drugs deducted from data	11(57.9)	5(26.3)	3(15.8)

To break down the information by hospital, the questions were split into 2 groups. Firstly, by factors which were likely to have a greater impact on the accuracy of pharmacy dispensing data – these were the exclusion of prescriptions at discharge and outpatient clinics. Secondly: by factors which probably had less influence on the accuracy of pharmacy dispensing data – these were the supply of all antibiotics by hospital pharmacy, and the deduction of wasted and returned antibiotics from pharmacy stock data. Only Y answers (positive) were counted and T answers (to some extent) were excluded. Three (16%) teaching hospitals (2, 4, and 10) had the most precise pharmacy dispensing data with Yes answers to all questions. Twelve hospitals (63%) responded Yes to both major factors from which 8 were teaching hospitals (57% from 14 total teaching) and 4 were non-teaching hospitals (80% from 5 total non–teaching Figure 8.3). This difference was not statistically significant (Chi-square with Yates' correction 2.1, $p>0.1$.

Figure 8.3: Precision of pharmacy dispensing data for measurement of antibiotic use by hospital inpatients. The maximum possible number of positive answers was two for major factors and three for other factors.



8.5.5 Antimicrobial management factors

Responses to this section of the questionnaire are summarised in Table 8.4 and Figure 8.5. Ninety-five % (n=19) of the hospitals had Infection Control Committees and 75% (n=15) had an established Antimicrobial Management Group. In 80% (n=16) of hospitals there were locally developed antibiotic formulary and guidelines. In 60% (n=12) of hospitals the guidelines were available electronically. In 70% (n=14) of the hospitals the microbiology test results were available in electronic format. In 26 % (n=5) of hospitals electronic prescribing for antibiotics was in use, however in most of the hospitals (58%, n=11) there was no form of electronic prescribing. In 16% (n=3) of the hospitals this system was in place for specific antibiotics. There was only one hospital with an online and patient specific decision support system for antibiotic prescribing. In 60% (n=12) of the hospitals there was regular feedback to physicians

about antibiotic use and resistance, while in 40% (n=8) there were no established systems for audit and feedback. None of the hospitals had financial incentives or penalties for physicians related to their performance on antibiotic prescribing or infection management. Most 60% (n=12) of the hospitals conducted special sessions on antibiotic prescribing for final year medical students or junior doctors as a part of their education, while in the other 40% (n=8) there were no education programmes on antibiotic prescribing. Most hospitals had interventions to improve antibiotic prescribing, in 35% (n=7) these were continuous and in 30% (n=6) the interventions were not intermittent. However 35% (n=7) of hospitals reported no interventions. In 40% (n=8) of the hospitals restriction policies were in place for specific antibacterials and in 45% (n=9) there were no restrictions on antibiotic prescribing.

Table 8.4: Antibiotic prescribing management factors. Y: Yes, N: No, T: To some extent

	Number of hospitals (percentage from total number of hospitals)		
	Y	N	T
Infection management committee	19(95)	1(5)	0
Antibiotic management group	15(75)	4(20)	1(5)
Local formulary/guidelines on use of antibiotics against diagnosis	16(80)	3(15)	1(5)
Electronic antibiotic policy/guidelines	12(60)	7(35)	1(5)
Online and patient specific decision support system for antibiotic prescribing	1(5)	19(95)	0
Regular feedback to physicians on antibiotic use and resistance	12(60)	4(20)	4(20)
Electronic prescribing	5(26)	11(58)	3(16)
Electronic microbiology results	14(70)	3(15)	3(15)
Financial incentives for the physicians based on their prescribing	0	20(100)	0
Antibiotic prescribing training for medical students and doctors targeted at antibiotic prescribing as a part of their education or on a regular basis?	12(60)	8(40)	0
Intervention to improve antibiotic prescribing	7(35)	6(30)	7(35)
Restrictions in supply of medicine e.g. a restricted drug procurement list against an approved formulary, stop orders	8(40)	9(45)	3(15)

This section included 12 questions. Number 1 and 0.5 were assigned to two possible positive responses: ‘Yes’ and ‘To Some Extent’ respectively. Hospitals 4 (9.5), 11 (9),

13 (8.5), and 1(8) had higher positive responses. Hospital 20 had the lowest score of 2.5. The mean of the scores was 6.7 ± 1.8. It seems that there were fewer variations in this group of responses than other groups, however, statistically the standard deviation is not very indicative of variation when the maximum score is limited to 12 or even 11 (none of the hospitals had financial incentive policies). The mean score for teaching hospitals was 6.9 and for non-teaching hospitals was 5.8 (Figure 8.4).

Figure 8.4: Antibiotic management factors. 'Yes' answers were regarded as 1 and 'To some extent' as 0.5. Total number of non-negative answers was added up for each of the hospitals.

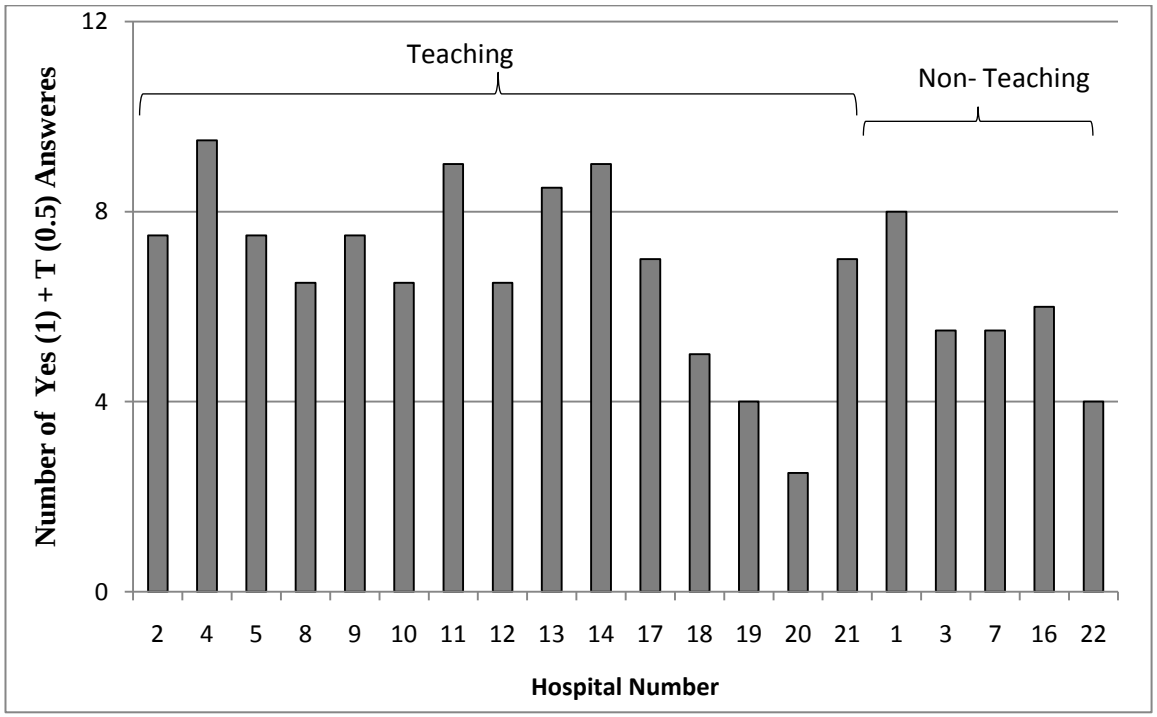
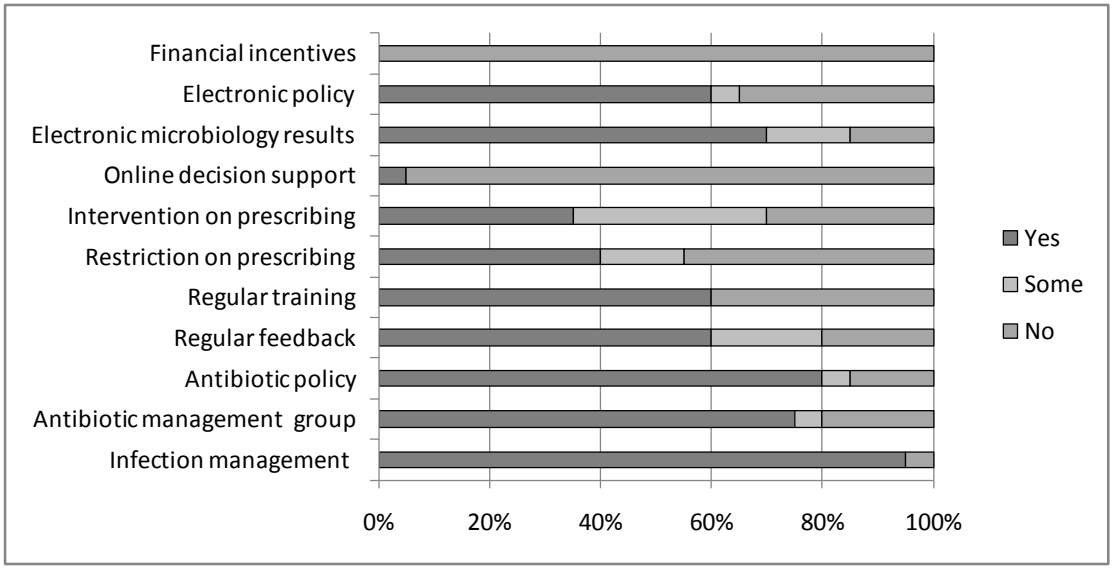


Figure 8.5: Antibiotic management factors aggregated for all hospitals given with the percentage of hospitals.



8.5.6 Association between antibiotic use and hospital characteristics

A simple regression was performed to assess the impact of hospital characteristics on hospital antibiotic use. Two measures of hospital antibiotic use were used separately: prevalence (% of patients receiving antibiotics on the day of the 2006 PPS) total antibiotic use in (DDD per 100 bed days in 2005). Since pharmacy dispensing characteristics are irrelevant to the number of treated patients in the PPS, this part of the questionnaire was excluded from PPS regression. The results are presented for significant regression coefficients and for two pre-specified variables: % of high user beds (Haematology/Oncology, ICU, Infectious Diseases, Organ Transplant, Renal Dialysis) and % of paediatric beds.

The percentage of ID beds, number of ID physicians, number of microbiologists and the presence of electronic prescribing were associated with higher prevalence of antibiotic use in PPS 2006. The presence of a training programme for medical students and doctors targeted at antibiotic prescribing as a part of their education or on a regular basis

in year 2005 was associated with lower prevalence antibiotic use in PPS 2006 (Table 8.5).

The number of organ transplant beds, and microbiologists was associated with higher total antibiotic use in DDD/100 beds in 2005. An antibiotic prescribing training programme for medical students and junior doctors was associated with lower total antibiotic use in 2005 (Table 8.5).

The % of high user beds did have a positive association with antibiotic use measured by prevalence in 2006 or total use in 2005 (Table 8.6). However, association was weak and not statistically significant. As expected there was a negative association between % of paediatric beds and total antibiotic use in DDD in 2005 but this was not statistically significant (p=0.174). There was a weak positive association between % paediatric beds and prevalence of antibiotic use in 2006 (p=0.067, Table 8.6).

Table 8.5: Univariate regression analysis for independent variables: ratio patients received antibiotics/admissions and antibiotic in PPS, and use in DDD/Bed with hospital characteristics. Only significant results are reported.

Dependent Variable	Independent Variable	Number of hospitals included in the analysis	Regression Coefficient	P-Value
Treated patients/admitted, PPS 2006	Percentage of ID beds	16	0.003	0.001
	Number of ID physicians per 100 bed	18	0.014	<0.001
	Number of microbiologist per 100 beds	18	0.102	<0.01
	AB prescribing training	18	-0.09	0.03
	Electronic prescribing	18	0.062	<0.01
Antibiotic use in DDD/Bed, 2005				
	Percentage of organ transplant beds	13	150.6	<0.001
	Number of microbiologist per 100 beds	18	223.9	0.04
	AB prescribing training	18	-266.94	0.04

Table 8.6: Regression analysis of antibiotic use measured as prevalence in PPS 2006 or total use in DDD/100 beds for 2005 over % of High User beds or Paediatric beds. High user beds were Haematology/Oncology, ICU, Infectious Diseases, Organ Transplant and Renal Dialysis

		Prevalence PPS 2006	Total Use LS 2005
High user beds with Hospital 5	Regression coefficient	0.004	1.7
	P value	0	0.6
High user beds without hospital 5	Regression coefficient	0.003	8.1
	P value	0.3	0.6
Paediatric beds	Regression coefficient	0.005	-8.4
	P value	0.07	0.2

Pairwise correlations with a level of observational statistical significance are presented in Table 8.7. Hospitals with a higher ratio of ICU beds were more likely to have a higher percentage of paediatric beds. There was a negative association between the percentage of ICU beds and the supply of all antibiotics by hospital pharmacy. The percentage of ID beds had a positive correlation with the number of ID physicians/100 bed (correlation coefficient =1, P- value 0.000) and with the number of microbiologists /100 beds. In hospitals with a higher ratio of ID beds the outpatient prescriptions were more likely to be excluded from pharmacy stock data. The ratio of paediatric beds had a negative association with the supply of all antibiotics by hospital pharmacy. This correlation has little value since there were 2 hospitals whose hospital pharmacy did not supply all the antibiotics. Electronic prescribing systems for antibiotics were more likely to be present in hospitals with a higher proportion of paediatrics beds. The percentage of renal beds and haematology beds were positively associated. The percentage of haematology beds was positively correlated with the percentage of organ

transplant beds, exclusion of prescription at discharge and outpatient dispensing, and existence of AMG in the hospital. The percentage of ID physicians had a positive correlation with the percentage of microbiologists but a negative correlation with the exclusion of the supply of antibiotics to outpatient clinics in pharmacy stock data. The ratio of infection control nurses had a negative association with the existence of ICC but a positive association with having electronic microbiology results systems in the hospital. In hospitals with a higher percentage of microbiologists it was less likely that returned drugs were deducted from pharmacy dispensing data. Hospitals with a higher percentage of microbiologists were more likely to have interventions to improve antibiotic prescribing. The number of beds was higher in teaching hospitals. Larger hospitals were more likely to have restriction policies on prescribing antibiotics and less likely to have electronic microbiology test results. Hospitals with a higher proportion of pharmacists were more likely to have electronic antibiotic guidelines and policies. The number of pharmacists/100 bed had a negative correlation with being a secondary or tertiary hospital. The number of pharmacists /100 beds had a negative association with the presence of an established AMG group.

Table 8.7: Pairwise correlations between the hospital characteristics. Only the significant correlations are reported.

	Pair of variables		Correlation coefficient, P-Value, Number of observations
1	% ICU beds	% Paediatrics beds	0.52,0.02, 19
2	% ICU beds	All antibiotics by hospital pharmacy	- 0.64, 0.003, 19
3	% ID beds	Number of ID physicians/100 bed	1, 0.000, 18
4	% ID beds	Microbiologists/100 beds	0.77, 0.000, 18
5	% ID beds	Outpatient prescriptions excluded pharmacy stock	-0.55, 0.2, 17
6	% Paediatrics beds	All antibiotics by hospital pharmacy	-0.66, 0.003, 18
7	% Paediatrics beds	Electronic prescribing	0.49, 0.04, 18
8	% Renal beds	%Haematology beds	0.53, 0.05, 14
9	% Renal beds	Patient pay for prescription	0.52, 0.04, 16
10	%Haematology beds	% Organ transplant beds	0.56, 0.04, 14
11	%Haematology beds	Discharge Excluded from pharmacy stock data	0.51, 0.05, 16
12	%Haematology beds	Outpatient prescriptions excluded pharmacy stock	0.52, 0.04, 16
13	%Haematology beds	Antibiotic management group	0.53, 0.03, 17
14	ID physician %100 beds	Microbiologists/100 beds	0.79, 000, 20
15	ID physician %100 beds	Outpatient prescriptions excluded pharmacy stock	-0.52, 0.02, 19
16	Infection control nurses/ 100	Infection management committee	-0.84, 0.00, 20
17	Infection control nurses/ 100	Electronic laboratory results	0.44, 0.05, 20
18	Microbiologists/100 beds	Returned drugs are deducted from dispensing data	-0.55, 0.01, 19
19	Microbiologists/100 beds	Intervention	0.53, 0.02, 20
20	Number of beds	Teaching	0.49, 0.03, 20
21	Number of beds	Electronic laboratory results	-0.57, 0.01, 20
22	Number of beds	Restriction policy on prescribing antibiotics	0.49,0.03, 20
23	Number of pharmacists/100	Secondary or tertiary	-0.50, 0.03, 19
24	Number of pharmacists/100	Antibiotic management group	-0.58, 0.01, 19
25	Number of pharmacists/100	Electronic antibiotic policy and guidelines	0.44, 0.05, 19

8.6 Discussion

Strengths of this study are that it used two different measures of antibiotic use with central processing and checking of data and that the participating hospitals were involved in the design of the questionnaire about hospital characteristics. Weaknesses of the study are that the number of participating hospitals (n=20) was too small for multivariate analysis, complete data on use and questionnaires were only available for 16 (73%) of the hospitals and these hospitals were only able to answer the questionnaire for the previous year. The approach of the ESAC Hospital Care team was to collect high quality data from a small number of hospitals. However, the participating hospitals did not receive any additional funding for data collection and the results show the limitations of what can be achieved even with support for central data processing and analysis. The lack of readily available longitudinal data about hospital characteristics is likely to be a serious limitation for future surveillance studies that seek to explain variations in hospital antibiotic use. In larger, multinational studies such as ARPAC[312] the advantage of increased sample size is offset by concerns about data quality.[183] Regional or national networks of hospitals have been able to collect reliable data about antibiotic use[161, 190, 315, 316] but only one study has also included detailed data about hospital characteristics from multiple hospitals.[315] Collection of standardised, longitudinal data about hospital characteristics should have a higher priority in antibiotic surveillance.

The ARPAC (Antibiotic Stewardship And Consumption) project published their findings from the questionnaire survey form 170 European hospitals.[312] In ESAC-2 hospitals, included in this chapter, 75% of hospitals had an Antibiotic Management Group (AMG) which is higher than 52% of the hospitals in the ARPAC study. Local antibiotic formulary guidelines were in place in 80% hospitals in the present study

whereas it was 77% with antibiotic formulary and 57% with antibiotic policy in ARPAC study. It seems that hospitals in the ESAC studies had more antibiotic control measures in place than the hospitals included in ARPAC study. In general, responses to detailed antibiotic management factors were similar across the ESAC hospitals. Only four (out of 12) factors had a prevalence of <50%; electronic prescribing, intervention, online decision support. Teaching hospitals had a wider range of antibiotic management scores compared to non-teaching hospitals with a bigger mean (Figure 8.4). Therefore, teaching hospitals had more organisational support. However, in nearly half of hospitals (47%) and 60% of teaching hospitals the number of pharmacists was less than the average in European hospitals or 0.93%. [333] For example, hospital 2, a university and non-ID hospital in a western European country, was one of the extremely high antibiotic users in the PPS and LS, while this hospital had the lowest number of pharmacists 0.17/100 beds, <1/5th of the average number of pharmacists in the European countries. In six (30%) of hospitals there were no ID physicians. Guidelines on antibiotic stewardship emphasise the importance of pharmacists and ID physicians. [148] [46]

Five specialties were identified likely to be associated with higher antibiotic use (Haematology/Oncology, Infectious Diseases, Intensive Care, Renal Dialysis and Organ Transplantation). It was also expected that the % of paediatric beds would be associated with lower antibiotic use measured in DDD because prescribed daily doses for children are usually lower than the WHO DDD. The variance in high antibiotic use beds (dispersion 150%) and paediatric beds (dispersion 100%) was considerably greater than the variance in total beds (dispersion 65%). Nonetheless there were only weak, non significant associations between either of the measures of antibiotic use and either % of "high user" bed or % of paediatric beds. However, number of Organ Transplant beds was associated with higher total use in 2005. The interpretation of the results for

paediatric beds is limited by an outlier (Hospital 2), the hospital with highest paediatric beds and with high use of antibacterials in LS 2005 and in PPS. Another likely explanation for these results is interaction (Table 8.6). For example, there was a significant positive correlation between the % of paediatric beds and % ICU beds or electronic prescribing. Hospitals with electronic prescribing had significantly higher total use than other hospitals (Table 8.3) so this plus % ICU beds is likely to have balanced the effect of % paediatric beds. Similarly the % of high user beds (e.g. Haematology) was positively associated with two Pharmacy characteristics: discharge prescriptions and outpatient prescriptions excluded from pharmacy stock. This means that antibiotic use in hospitals with lower % of haematology beds would be biased (over estimated) by inclusion of data about antibiotics dispensed at discharge or to outpatients. There were also potentially important interactions between the number of antibiotic specialists (ID Physicians, Microbiologists, Pharmacists) and variables that were associated with higher antibiotic use (Table 8.6). All of these findings suggest that meaningful analysis of hospital characteristics will require multivariable analysis.

One positive finding from this study was that training on antibiotic prescribing for medical students and doctors as a part of their education was associated with lower antibiotic use by both measures, prevalence in 2006 and total use in 2005 (Table 8.6). However, this finding requires further validation, preferably through intervention studies. Overall the results of the present study demonstrate three key limitations of observational data for evaluation of the impact of antibiotic control measures. The first limitation is that the hospitals were unable to provide information about the timing or duration of the antibiotic control measures. The second limitation is that in this study equal weights were given to all antibiotic management factors by assigning of 1 to all Yes responses, whereas some measures may have more impact than most. A third

limitation is that the presence of a control measure does not mean that it has been implemented effectively. For example, an AMG is said to be critical for antibiotic policy, interventions, training, and audit and feedback[46] the presence of an AMG does not guarantee that any of these interventions actually occur. For example, hospital 9 had no AMG but did have training, audit and feedback and interventions whereas hospital 3 had an AMG but no training programme and non-continuous audit and feedback. It can be concluded that an established AMG does not necessarily equal a dynamic leadership in antibiotic management, which may explain why there was no correlation between AMG and total use of antibacterials. The final and arguably most important limitation is to question whether total use of antibiotics or prevalence of antibiotic use are good indicators to evaluate an AMG or other antibiotic control measures. The ARPAC study also found no correlation between total antibiotic use and the presence of an AMG, antibiotic policy or formulary. [312] However, in the same study the same antibiotic control measures were all correlated to lower use of Cephalosporins, Macrolides, third generation Cephalosporins and Aminoglycosides. [312] It is likely that antibiotic prescribing management factors (Table 8.4) will be targeted at specific antibiotics or infections and are therefore better evaluated with intervention studies and more specific outcomes. Valid evaluation can be achieved with quasi-experimental designs including interrupted time series analysis.[148, 276]

8.6.1 Study limitations

The questionnaire did not include the impact of the pharmaceutical industry but advertising and promotion by the pharmaceutical industry is a major and powerful source of information for prescribers. [334] In a review of the literature on the interactions between physicians and the pharmaceutical industry, it was concluded that there was strong evidence that these interactions influence prescribing behaviour. [335]

In this study, with one hospital per country with differences in health care system, it is especially hard to make judgments based on the comparison of a teaching hospital in one country with a non-teaching hospital in another country.

Although the analysis of pairwise correlations was statistically justified, it can be affected by a low number of observations and high variations and the outlier hospital 5 with the highest number of ID beds and ID physicians. If this hospital was excluded, the number of observations would not only weaken the statistical analysis by reducing the number of hospitals, it could also undermine the nature of data that corresponded to variations in hospitals. Additionally, there might be other correlations that could not be justified by statistics. In categorical variables a common cause of variance restriction is binning of continuous data, by reducing the original full range to a finite set of categories such as high/medium/low.

For this set of hospitals there were none with financial incentives for prescribers and only one with online decision support systems. However, these variables may be important factors for a study with higher number of hospitals from all European regions.

8.7 Conclusion

Although limited to 20 hospitals this study has identified potentially important descriptive information about hospital structure that was not addressed in previous studies [312] or current European projects. [336]

The information collected revealed potentially important differences between hospitals in case mix, hospital pharmacy data, organisational factors, and antibiotic management measures. Furthermore, identified were potentially important interactions between these variables and suggest that future observational studies should be large enough to allow multivariable analysis. However, hospitals were unable to provide information

about these variables for more than one previous year and this is unlikely to change unless there are incentives for hospitals to collect and record the data. Future studies of determinants of hospital antibacterial use from multiple European countries will need to define a standard dataset to be collected prospectively.

CHAPTER NINE: CONCLUSION

In this thesis I improved and implemented a series of methods that arise when drug utilisation research (DUR) is used to evaluate and manage hospital antimicrobial use. I started to test and use the methods in Tayside followed by applying them to a set of European hospitals. For the European study, ESAC, the research hypotheses needed design and implementation of new methods to identify and overcome barriers to Europe–wide DUR of antimicrobials. In all studies in this thesis, clinical and hospital pharmacists had the central role in delivering the intervention and surveillances.

In Chapter one, 1.2, the literature review described the importance of antimicrobial use in general as a worldwide issue. Antimicrobials, like any other drug group, need regular research for their appropriate use. Nonetheless, antimicrobials are fighting transferable diseases and their inappropriate use has resulted in transferable collateral damage in the form of antimicrobial resistance and *Clostridium difficile* infections. The impact of these life threatening infections extends well beyond patients who receive antibiotics and they result in huge costs to the health care system. Inappropriate use of antimicrobials is also affected by inappropriate use in the community either in primary care or through over the counter use. Nonetheless, inappropriate use in hospitals is arguably a more important target for intervention because hospitals are confined environments with more vulnerable patients and intensive, prolonged antimicrobial use where cross-infection is more likely to occur. Standardised measurement of antibiotic use is an essential first step towards improvement of hospital antibiotic prescribing.

In Chapter 1-3, I reviewed different measure and methods of evaluating hospital antibiotic use and showed that no single method can capture all quality outcome measures. A combination of different methods can provide an accurate assessment of

hospital antimicrobial use and improve the reliability, discrimination and feasibility of the measures. Few hospitals in Europe have electronic systems that can capture information about antibiotic prescribing to individual patients. Nonetheless, patient specific DUR through point prevalence surveys (PPS) combined with longitudinal surveys (LS) of total use and hospital demographics can capture comprehensive information about antimicrobial prescribing practice that can be used to assess use over time or compare use in different geographic areas. Nonetheless, my literature review identified important gaps in evidence about measurement of hospital antibiotic use. The issues raised from previous studies showed that firstly, there are common inconsistencies in the methods together with misinterpretations and miscalculations. Secondly previous studies used single methods (either PPS or LS) to interpret hospital antimicrobial use. In previous LS studies there was no statistical analysis or the methods used were not appropriate for longitudinal time series. Finally, there was unresolved debate about methods for adjustment for clinical activity. These gaps in the evidence about assessment of hospital antimicrobial use were addressed in this thesis. In Chapters 3 and 5 to 8, I applied the WHO ATC/DDD methods for drug classification and measurement. However, through point prevalence survey I was also able to document PDD (prescribed daily dose) in order to assess antimicrobial prescribing against patient and disease specific guidelines.

In Chapter 2, time series analysis (TSA) and interrupted time series analysis (ITSA) methods, were reviewed and described. By documenting the methodological and statistical issues in application of TSA and ITSA this chapter provides potential resources for researcher and policy makers. The ITS and TSA techniques used in this thesis have rarely been applied to published studies of hospital drug use. The ITSA method in chapter 3 used to assess the use and cost of the intervention reflected the gap

identified in review articles. [148, 236, 276] This study helped researchers to apply and improve method for evaluation of intervention and has been cited by 51 studies (ISI Web of Science 2009). One limitation of the study was lack of comparator for the study hospital. I implemented and improved my learning from ITS and TSA techniques for the statistical analysis of evaluating the impact of devolution in UK 1995 and increase in age exemption from prescribing charges in Wales in 2002 on antibacterial prescribing in primary care in four UK administrations with Belgium as the control country(cited 9 times in ISI Web of Science 2009, although only published in 2008).[337]

In Chapter 3, I used ITSA techniques and DUR study to evaluate the impact of Alert Antibiotics intervention in Ninewells hospital. I showed that evaluation of the intervention based on the clinical pharmacist records could be biased because there was no way to conceal allocation after the intervention and because very little data had been collected before the intervention. Longitudinal analysis for two years before and after the intervention required record linkage between pharmacy stock data and clinical activity data. It was time consuming and laborious since no systems were in place before this study. The recommendations from this study were implemented in two other projects. This study supported the intervention team, Tayside Antibiotic Subcommittee, to add a new tool for continuation of antimicrobial stewardship programmes in Tayside. Hence, I established records linkage assigned with the WHO ATC/DDD methodology for all anti-infectives included under BNF chapter 5 for Ninewells and Perth Royal Infirmary hospitals at hospital ward and clinical group during 1999- 2004. The written program was then embedded to regular pharmacy stock data. Preliminary reasons was firstly, to evaluate the use and cost of Alert Antibiotic intervention on a continuous basis and secondly, to extend DUR from Ninewells to Perth Royal infirmary and thirdly, to put a system in place for regular feedback to clinical groups and evaluate

interventional programmes. Results were reported to Tayside Antibiotic Subcommittee and presented in conferences. The regular DUR system allowed further research. [275] Having established the record linkage producing DUR of all anti-infectives was then used in a change programme for continuous quality improvement (CQI). I collaborated to this phase, as the Quality Improvement Co-ordinator for Antibiotic Prescribing as a member of Steering Group. During this time the Alert Antibiotic intervention was re-launched, quarterly DUR reports were provided for each Clinical Directorate in their meetings, area of more concern were highlighted for future interventions. Under supervision of the CQI Steering group, I used statistical process control (SPC) as a simple tool to monitor antimicrobial resistance. I tested the PDSA (Plan, Do, Study, ACT) as recommended by IHI (Institute for Healthcare Improvement) as simple interventional tool. Finally, I contributed to establishment of Scottish Antimicrobial Group. This Tayside experience contributed to a governmental recommendation [338] and further improvement in hospital antibiotic prescribing in Scotland. [339]

In Chapters 5 and 6 I applied TSA to pharmacy stock data and clinical activities. In Chapter 5, the preliminary aim was to assess whether two denominators of clinical activity (admissions and bed-days or patient-days) may affect total use. Furthermore, length of hospital stay and discharge were also estimated and included in regression model. All outcomes were used to group the hospitals. In chapter 6 through a series of complex statistical processes the trends in use of parenteral antibacterials, and Quinolones and third generation Cephalosporins were extracted and normalised by constants to produce the “change” rather than “time trends” so that the hospitals could be compared. One key finding from these two chapters was that more than one clinical activity variable should be used to interpret changes over time. Processing hospital data at product level, as mentioned in Chapter 5, was too laborious and time consuming.

After submission of the first report to ESAC in summer 2006, I re-validated databases several times so that the database became ready in November 2008. However, I still encountered problems with outliers and structural breaks as described in Chapters 5 and 6.

In Chapter 7, the ESAC PPS I applied a statistical method for calculation of confidence intervals for ranking and concluded that this method should be applied in future comparison between organisations for their performance indicators. The PPS chapter provided additional indicators of hospital antibiotic use. The comparison of some of LS (pharmacy stock data) and PPS (patient specific data) outcomes for example: total use, proption of each drug from total use, proportion of use of parenterals and broad – spectrum antibacterials after preliminary analysis were included in the report to ESAC and comprehensively presented for participating hospitals and are presented in the Appendix. Nonetheless, there were too few hospitals to allow statistical analysis so these results were not included in the main body of the thesis. The findings from chapters 5, 6 and 7 confirmed that no single measure can be used to evaluate antibiotic prescribing practice in hospitals.

In Chapter 8, I showed that differences in hospital characteristics may explain some of the between hospital variation in antibiotic use identified in Chapters 5-7. Nonetheless, lack of available longitudinal data about hospital characteristics is likely to be a serious limitation for future surveillance studies that seek to explain variations in hospital antibiotic use. Furthermore the presence of an antibiotic control measure does not mean that it has been implemented effectively. The study emphasises that central data collection and processing about hospital characteristics, case mix, and functionality of control measures is as important as central processing of antimicrobial use data.

In conclusion, this thesis provided evidence that there is no "gold standard" for measurement of hospital antimicrobial use.

I provided feedback of the results, covering more topics than those discussed in this thesis, to ESAC-2 participating hospitals within the preliminary report and various meetings. By the end of the project and when ESAC-3 was launched, I designed a questionnaire and asked the ESAC-2 team to reflect on their experience from participating in ESAC-2 and the results of the study. The common points raised from reflections were:

- They presented the report in their hospitals or at regional and national level and got organisational support for continuous audit and feedback.
- They implemented measurement of the duration of surgical prophylaxis in their regular audit and interventional studies at hospital or national level
- They compared their results with other ESAC hospitals and presented these in their institutions
- They found PPS very useful, easy to perform and have continued to use this method following the ESAC 2006 PPS

The ESAC studies described in this thesis supported the ESAC project to continue and apply ESAC-2 methods to a larger number of European hospitals. [253, 254, 256, 257, 340] The experience from the Scottish hospital, from ESAC-2 was implemented across Scotland by the Scottish Antimicrobial Prescribing Group (SAPG) as the Hospital Medicines Use Database, launched in April 2010 (http://www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Management/References/2010---June/14/Development-of-a-system-to-allow-comparison-of-Secondary-Care-medicines-utilisation-across-

Scotland/). SAPG used the same indicators recommended in the PPS chapter and set two targets for continuous quality improvement of hospital antimicrobial use across Scotland (>95% compliance with surgical prophylaxis <24h and with all empiric antibiotic prescriptions in medical or surgical admission units being compliant with local antibiotic policy) . They also decided to use pharmacy stock data for LS which are analysed centrally at national level. [341] [342, 343]

What I learned from this thesis

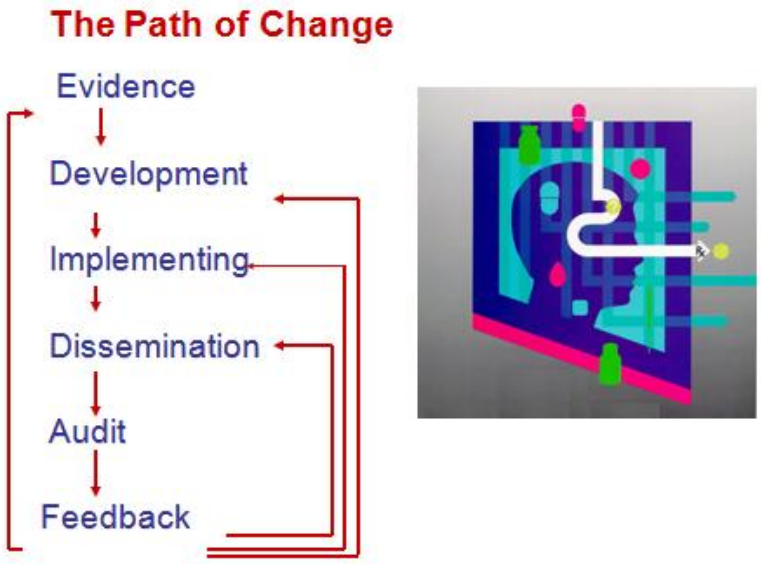
In this thesis I learned a series of analytical and statistical methods for each of the chapters. I established regular DUR and feedback to clinicians and participated in a change programme in health system across Europe. The foundation of standard DUR reports for Tayside took one year. I applied and extended the findings to 20 hospitals in different European countries. For this project, data were analysed centrally mainly by myself. The databases were so different and laborious to work on that took more than 2 years to make them ready for a PhD thesis. Nonetheless, there is still uncertainty about raw data. Administrative data result in errors that can be very large because of multiplication factors. Additionally, even very extreme results in this thesis were not identified as being implausible by the staff responsible for data entry. Comparison across countries and hospitals therefore requires both careful training of local data collectors, and a central checking process. Pharmacy stock data and clinical activity data should be analysed centrally by each country and where the country has a large population by regions. The ESAC project was unable to apply this possibly because of the limited budget. Nonetheless, if the surveillance of hospital antibiotic is a global issue, the European Union and EU countries should allocate more resources to establish national or regional networks with central data processing. The national networks for centralised process and analysis of hospital antimicrobial have been established in Sweden, Norway, and Netherlands. In Scotland, SAPG and ISD (Information Services Division) have worked together to establish national antibiotic surveillance that can be linked to microbial surveillance through Health Protection Scotland. The task of the central data process will be much easier for specialised computer programmers than for researchers.

During and after the ESAC- PPS 2006 with face to face feedback and discussions during ESAC, I learned that the structure of survey team affects collected data. Additionally, in one hospital one person performed the PPS whereas in another a multi-professional team consisted of 20 members did the survey. The information of the survey forms was entered into STRAMA by different people that in some cases had to estimate uncompleted information. During set up the ESAC-3 proposal and after several feedback meetings, I found that even people from the same research background are different in their perceptions from a simple PPS form.

Therefore, I conclude that DUR researchers should be supported by mathematicians, statisticians, econometricians, social scientists, and qualitative researchers.

Finally, I learned that big studies, specially concentrating on total antimicrobial use are not enough. DUR researchers need to move from big studies with big targets to interventional studies with simple and easy but clinically important outcomes. As presented in Figure 9.1 improvement in hospital antimicrobial use like other health care change programmes consists of linked components. Although, big studies like ESAC are successful in identifying the gaps and improve indicators of antimicrobial use, they need to be implemented and improved and translated into local needs. Clinicians are supported with published evidence and guidelines. Nonetheless, simple and easy audit and interventional tools like SPC and PDSA can produce more meaningful evidence for them in their daily practice.

Figure 9.1 The Path of Change



Recommendations for further studies

The methods developed in ESAC-2 have the potential for further studies. Evaluation the use of Alert Antibiotics can provide use of reserved antibacterials between European hospitals. This study is suggested for LS and PPS data. In this thesis I did not compare the detailed utilisation pattern of antibacterials across the hospitals. However, I have contributed to paper entitled "Drug Utilization 75% (DU75%) in 17 European Hospitals (2000 - 2005)" ESAC-2 Hospital Care Sub Project" which is submitted currently.[344] To implement a more comprehensive indicator of antibacterial use it was more appropriate to apply DU90% to capture the bigger bulk of use. Nonetheless, for this manuscript with large number of hospitals it was technically difficult to include all antimicrobials in DU90% segment for one publication.

From PPS data further analysis are suggested for use of antibacterials therapy in SSTBJ (skin, soft tissue, bone and joint) and for urinary tract infection.

In this thesis the potentially important interactions between hospital characteristic variables and use of antibacterials were identified. Number of hospitals in ESAC-2 project was small therefore, it is suggested to include enough hospitals in future studies to allow a multivariable and multilevel analysis.

For future interrupted time series analysis, depending on study aims and design and when sufficient data are available use of control group may be appropriate.

Key findings

- Patient specific data (PPS) together with LS and hospital demographic can capture comprehensive information about antibiotic use
- Statistical methods should be used in future DUR studies
- Central data processing is important for minimising errors but is time consuming and is not available in most European countries
- Lack of accurate longitudinal data and hospital characteristics limits the ability of observational studies to explain variation in antibiotic use
- DUR researchers need to move from big observational studies to focused, interventional studies.

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APPENDIX A.4: **ESAC II- PROTOCOL FOR HOSPITAL CARE SUBPROJECT (HC), VERSION 3 JANUARY 2006**

Background

In 2004 DG SANCO of the European Commission supported a second phase of the ESAC project for 2004-2007. The aim of the ESAC II project is to deepen the knowledge of antibiotic consumption in four specific areas: ambulatory care, hospital care, nursing homes and socioeconomic determinants of use.

The aims of the ESAC II project are:

- To consolidate the continuous collection of comprehensive antibiotic consumption data in all European countries which was established in ESAC I.
- To develop health indicators of antibiotic use based on consumption data, to validate these indicators, and to use a set of core indicators to give feedback of the antibiotic consumption in the participating countries.
- To deliver economic data on antibiotic consumption.

The Hospital Care Subproject

Within the ESAC I project it was recognised that there is currently no unified hospital information on antibiotic use across the European countries. The explanations include lack of standardised methods for producing valid data either for hospital antibiotic use or for denominator data related to clinical activity, such as occupied bed days or admissions. A recent study from the Netherlands suggested that an apparent increase in total antibiotic use from 1997 to 2001 was eliminated when the denominator was admissions rather than bed days. [1] The explanation was that there had been an increasing number of admissions over the period with decreasing mean length of stay.

In order to prepare and agree on detailed objectives, methods, and recruiting meetings have been held in February 2005, June 2005, Sep 2005 and January 2006. Future meetings will be held on Sunday 2nd April 2006 from 12:00-14:00 during 16th ECCMID meeting in Nice where the final software will be demonstrated. ESAC cannot provide funding for this meeting, but will organise the meeting room. Most probably there will be a final meeting at ECDC in Stockholm in September 2006.

ESAC II- HC will focus on consistent data collection from individual hospitals in order to develop a standard method that can be rolled out to other hospitals in the participating countries. The project will start with one hospital in each of 23 countries.

Structure

Members of ESAC II- HC come from 23 countries: Austria, Belgium, Croatia, Czech, Republic, Denmark, Estonia, Finland, France, Greece, Germany, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Slovenia, Sweden, Turkey and the four countries of the UK (England, Northern Ireland, Scotland and Wales). From participating hospitals two hospitals (Lithuania and Malta) will participate in point prevalence study

and one-year (2005) longitudinal study and another hospital (Wales) will participate in longitudinal study only.

The Project is lead by Prof Peter Davey from UK and co-ordinated with the ESAC project by Prof Herman Goossens. The data management team (Faranak Ansari and Angela Johnston) is based in the Health Informatics Centre at the University of Dundee.

Research Questions:

What is the trend in hospital antibiotic use over the study period?

What effect do different denominators (bed days or admissions) have on longitudinal analysis of hospital antibiotic use?

What is the relationship between the DDD calculated from total antibiotic use and the actual daily doses prescribed in each hospital?

Objectives & Deliverables

Objectives

1. Numerator definition
2. Denominator definition
3. Basic hospital statistics
4. Standardised data reporting
5. Identification of potential explanatory variables for future studies

Deliverables

1. Standardised longitudinal drug use data from at least one hospital per country
2. Checklists for good practice in reporting longitudinal data and intervention studies
3. Pilot web based methodology for point prevalence studies to measure use plus other patient specific data.
4. Strategy for regional and national roll out
5. Identification of potential explanatory variables and intervention targets for future research studies

Methods

Longitudinal Study

Setting

One hospital has been selected from each country (including one hospital each from the four UK countries, England, Northern Ireland, Scotland and Wales). For countries with pre-existing networks of hospitals the ESAC national representative has been asked to identify one hospital that will be able to support both the longitudinal and point prevalence components of the HC subproject.

Given that the main question of the study requires analysis of time trends in antibacterial use, the details of country and hospital demography are of lesser importance. Nonetheless, a questionnaire about country health-care system and hospital demographics was designed and agreed to identify potential explanatory variables in

future comparisons between countries or hospitals. No European benchmarking will be performed in this subproject.

Numerator: Antibiotic Use

The study will focus on systemic antibacterials in the J01 sub-class according to ATC classification by the WHO Collaborating Centre for Drug Statistics plus oral metronidazole, oral vancomycin and colistin.

Participants will provide number of dosage forms dispensed from hospital pharmacy to hospital as a whole. Minimum database requirements are:

- Dosage form with complete information on strength, package and route of administration

- The inpatient destinations for dispensing

- Preferably in generic name and in English language however French, Dutch and German language can be accepted.

The amount of each product will be converted to WHO Defined Daily Doses (DDDs). DDDs will be those which are current when the analysis begins. Any products without a WHO DDD will be assigned a temporary ESAC DDD.

Estimated PDD (Prescribed Daily Dose) will be provided by participant hospitals based on their local antibiotic policy or local or national formularies. These data will be compared with actual PDD data collected in the point-prevalence survey. It is anticipated that estimated PDDs will be inaccurate and that this information will be important in demonstrating the added value of cross sectional, point prevalence studies.

Denominator: Clinical Activity

The project will compare two denominators: bed days and admissions. It is anticipated that annual increments in antibiotic use will be less when the denominator is based on number of patients (admissions or discharges) *versus* number of bed days. [1]

We will ask hospitals to define the methods that they use to measure bed days or admissions. We anticipate that the following methods are in use but will record other methods if they arise.

<u>Bed days</u>

1. Occupied bed days (OBD) calculated from daily census of the number of occupied beds at a specified time (e.g. midnight).
2. Hospital care days calculated from daily census of the number of patients that have occupied each bed in a 24 hour period (can be >1 patient per day).
3. Patient days (based on length of stay, e.g. date of discharge-date of admission - 1)

<u>Admissions</u>

1. Does the number of admissions include day cases? If so can day cases be excluded? If not does the hospital have data about % day cases by year?
2. How are birth admissions included? Do they count as one admission or two? Has a consistent method been used throughout the study period?

Time period

Feb 06

Monthly data will be collected for 5 years starting from January 2000 until December 2005.

Use indicators- DDD/100 bed-days and DDD/100 admissions will be the study indicators.

Analysis- Time trends in antibacterial usage will be analysed for each participant hospitals within the 5-year period using time series analysis with statistical test for trend based on linear regression.

Point Prevalence Study

The STRAMA (Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance)[2] web based system for recording national Swedish point prevalence surveys will be used for the ESAC point prevalence survey. Mats Erntell has already worked with the Finnish company that maintains the software to produce an English language version:

https://www.neotide.fi/esac
Login: pps
Password: ****
To start the soft-ware: Login/password ****/****

The software has to be customized for each hospital that uses it based on their specialties and drug list. Therefore the pilot will be confined to one hospital per country.

A workshop for training on the methods for the Point Prevalence Survey and use of the web based software was organised in January 2006 in Prague. The hospital selected for the longitudinal study must also participate in the cross sectional point prevalence survey.

Participating hospitals will provide:

- List of specialties and subspecialties as administrative unit
- List of available antibacterials (ATC class J01, J04AB, A07A, P01AB) in the hospital, with ATC codes and route of administration. There are two columns for entering drug names. The generic name of the drug should be entered in English in Column 1 (e.g. amoxicillin, ciprofloxacin). The second Column should be used for the name that hospitals want to appear in the pull down menu for their web page when they enter data. This can either be one or more trade names for the drug or a translation of the generic name into their language. Hospitals also need to provide the maximum prescribed daily dose for each product. This will be used as an upper limit as a warning in the program but it will be possible to enter higher doses, so this should be the maximum dose that is likely to be prescribed for any patient.

When:

The survey should be completed during two calendar weeks between 1st April and 31st May 2006. Surgical wards should be surveyed on Tuesday, Wednesday or Thursday in

order to capture information about prophylaxis in the previous 24h. Medical wards can be surveyed on Monday, Tuesday, Wednesday or Thursday. Depending on the number of beds hospitals can decide to complete the survey over one or more days. However, all beds in each administrative unit (e.g. Internal Medicine, General Surgery) should be completed in a single day.

Who will perform:

The person should be familiar with reading patients notes (ID specialist, microbiologist, pharmacist, infection control nurse). Hospitals may decide to have a team of people with specialist expertise in microbiology or infectious diseases. The HC Hospital lead will be responsible for training other members of the team.

Who will be included:

All patients who are in the hospital at 8 am on the days of survey should be included in the study. The number of admitted patients at 8 am at the departments is entered in the special form.

Patients who are receiving antibiotics at 8am on the day of the survey should be identified and the details of prophylaxis or therapy recorded on the data sheet.

For surgical patients administration of prophylactic antibiotics should be checked in the previous 24h. If so the details will be recorded as surgical prophylaxis. The reason for this is to code the duration of prophylaxis as either C1 (one dose), C2 (one day) or C3(>1 day). This information is recorded in the "Indication" field on the data entry form and website.

What is the anatomical site of infection or prophylaxis?

The diagnose and indication for prophylaxis uses the same "diagnosis group", ie most often related to an organ - skin, lungs etc. The aim is to find out what the physicians think they are treating. For this we will look at all patient records, and may request additional information from nurses, pharmacists or doctors. There will be no discussion about the appropriateness of prescribing. The staff should not have the feeling that we are checking them and there is no intention to change prescribing.

Which drugs to include:

Systemic antibacterials in J01, J04AB, A07A and P01AB classes. Actual prescribed dose should be recorded both for adults and paediatrics for single and combination antibiotics (e.g. 960mg of co-trimoxazole).

Technical support

Prof Mats Erntell has kindly accepted to be the "help desk" for software problems during the PPS. The software will be hosted on the STRAMA server

Core data for the cross sectional point prevalence survey will be:

- Proportion of patients treated with antibacterials
- Patients' age and gender
- Antibiotic
- Dose per administration
- Number of doses per day
- Route of administration
- Anatomical site of infection or target for prophylaxis according to the list of diagnosis groups
- Indication for therapy (community acquired infection, hospital acquired infection or prophylaxis)

Possible optional fields:

- Immunosuppression
- Foreign material present
- Relevant culture before therapy
- Indication for given therapy in medical records
- Assessment of given treatment against local (hospital, regional or national) antibiotic policy

All of the fields (core and optional) are on the web based data record.

Fields must be recorded for all patients in the survey. Hence, for a hospital's data to be included in the PPS all of the core fields must be completed for all patients in the survey.

The decision about optional fields is entirely at the discretion of each participating hospitals and can be left until the time of the survey. If a hospital finds that it does not have the resources to complete an optional field for all patients in the survey then this field will not be included in the analysis for that hospital.

The training meeting reviewed pilot data from each of the participating hospitals and also used specimen cases for data entry at the meeting.

Dissemination

The results will be published on the ESAC website. The study team in Dundee and the STRAMA website will provide concurrent feedback to the participants and they will disseminate the results to their hospitals and local authorities.

The study will be published by the ESAC hospital subproject principle investigators with ESAC Subproject Group as co-authors. Feedback of the results for each hospital will be given to the country participants and they can publish their own individual hospital results with themselves as lead authors.

Timetable

The time schedule for the project is set out in Table 1 with progress achieved by the end of January 2006 coded with symbols:

Table 1: ESAC II- Protocol for Hospital Subproject (HC)- Time table				
	Heading	**Update:**	**Date Due**	**Status**
1. Set up the project needs				
1.1	Decide on communication policy	Group	7th Sep 05	✓
1.2	Confirmation of participant countries	Group	7th Sep 05	✓
1.3	Confirmation of participant hospitals	Group	7th Sep 05	✓
1.4	Confirmation of included drugs in the study	Group	7th Sep 05	✓
1.5	Design a questionnaire about country and hospital demographics	Dundee team, MF	30 Oct 05	✓
1.6	Providing the completed questionnaire	Group	15 April 2006	☺
1.7	Providing final software for PPS	Group plus STRAMA	1 April 2006	☺
2. Longitudinal Study				
2.2	Provide the Dundee team with a sample of database	Group	15 Oct 05	☺
2.3	Communication to clarify database specifications for Dundee team	Dundee team, Group	15 Oct 05 – Apr 06	☺
2.4	Send monthly pharmacy data from January 2000-Decmber 2005	Group	01 Feb- 01 April 06	×
2.5	Send monthly admissions and occupied bed day data Jan 2000-Dec 05	Group	01 Mar- 01Apr 06	×
2.6	Sending the PDDs for the systemic antibacterials	Group	01 Mar- 01Apr 06	×
2.7	Data process and analysis	Dundee team	01Apr-01Oct 06	×
2.8	Final report	Dundee team	01 Dec 06	×
2.9	Dissemination on ESAC website	ESAC team	01 Feb 07	×
2.10	Manuscript Submission	Group	01 Mar 07	×
3. Point Prevalence Survey				
3.1	Confirmation of participant countries	Group	Dec 2005	☺
3.2	Confirmation of participant hospital from each country	Group	Dec 2005	☺
3.3	Drug list and specialty list sent to Mats Erntell at STRAMA	Group	20 February 2006	☺
3.4	Completion of entry of five cases per hospital to prepare for the training meeting	Group	23 Dec 2005	?
3.5	PPS Training Workshop	Group plus STRAMA	Q1 06	✓
3.6	PPS Training Workshop (at ECCMID)	Group plus STRAMA	April 2006	☺
3.7	Data collection	Group	April-May 2006	×
3.8	Data process and analysis	Dundee Team	Q3 06	×
3.9	Final report	Dundee Team	01 Dec 2006	×
3.10	Dissemination on ESAC website	ESAC team	01 Jan 2007	×
3.11	Manuscript Submission	Group	15 Feb 07	×

Key to Implementation Status	
✓ – Action completed	? – Not known, further information required
☺ – Action on course for completion	□ – Change to action originally planned
⌛ – Progress made but slippage on planned timescale	□✂ – Decision not to progress
✖ – Little or no progress achieved	

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Appendix A.5.1: Tables of Time Series Plots

Table A.5.1.1: Plots of antibiotic use in DDD or Y over time for all hospitals

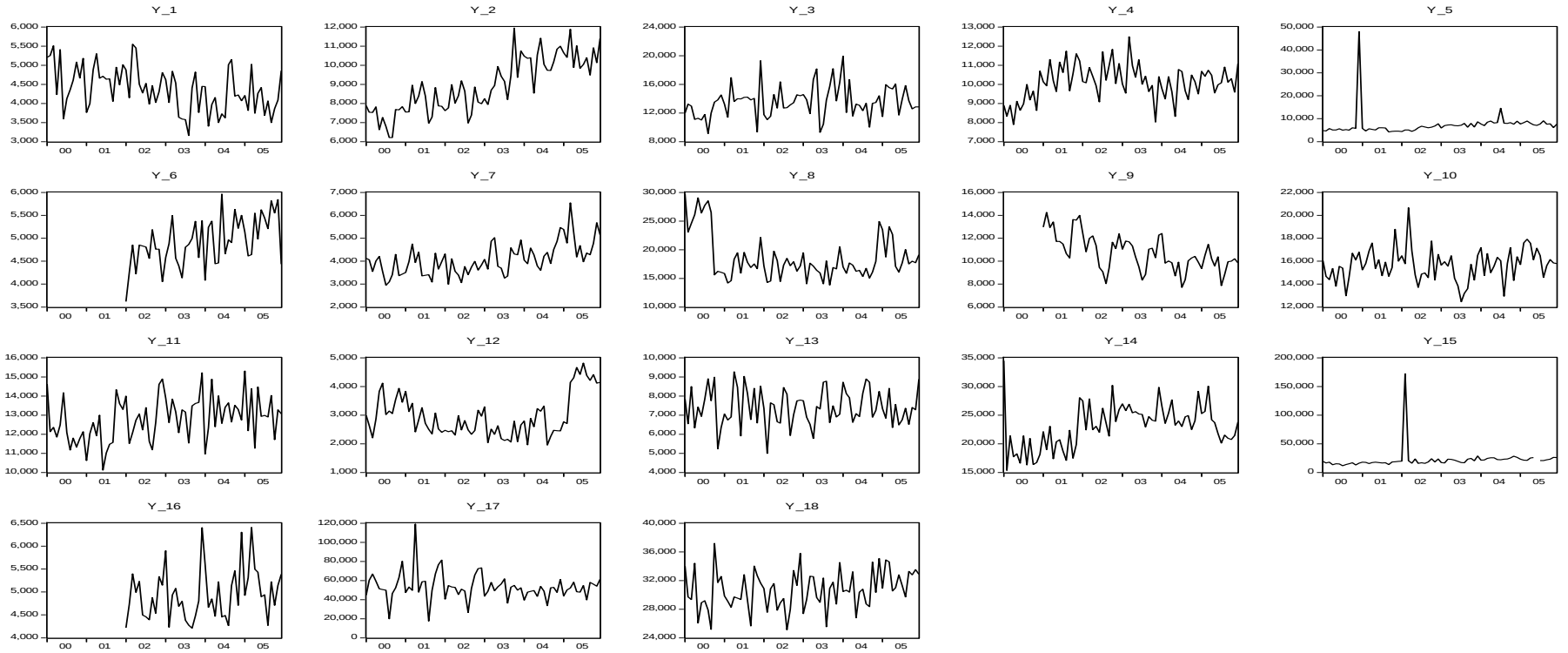


Table A.5.1.2- Plots of Bed-days or B over time for all hospitals

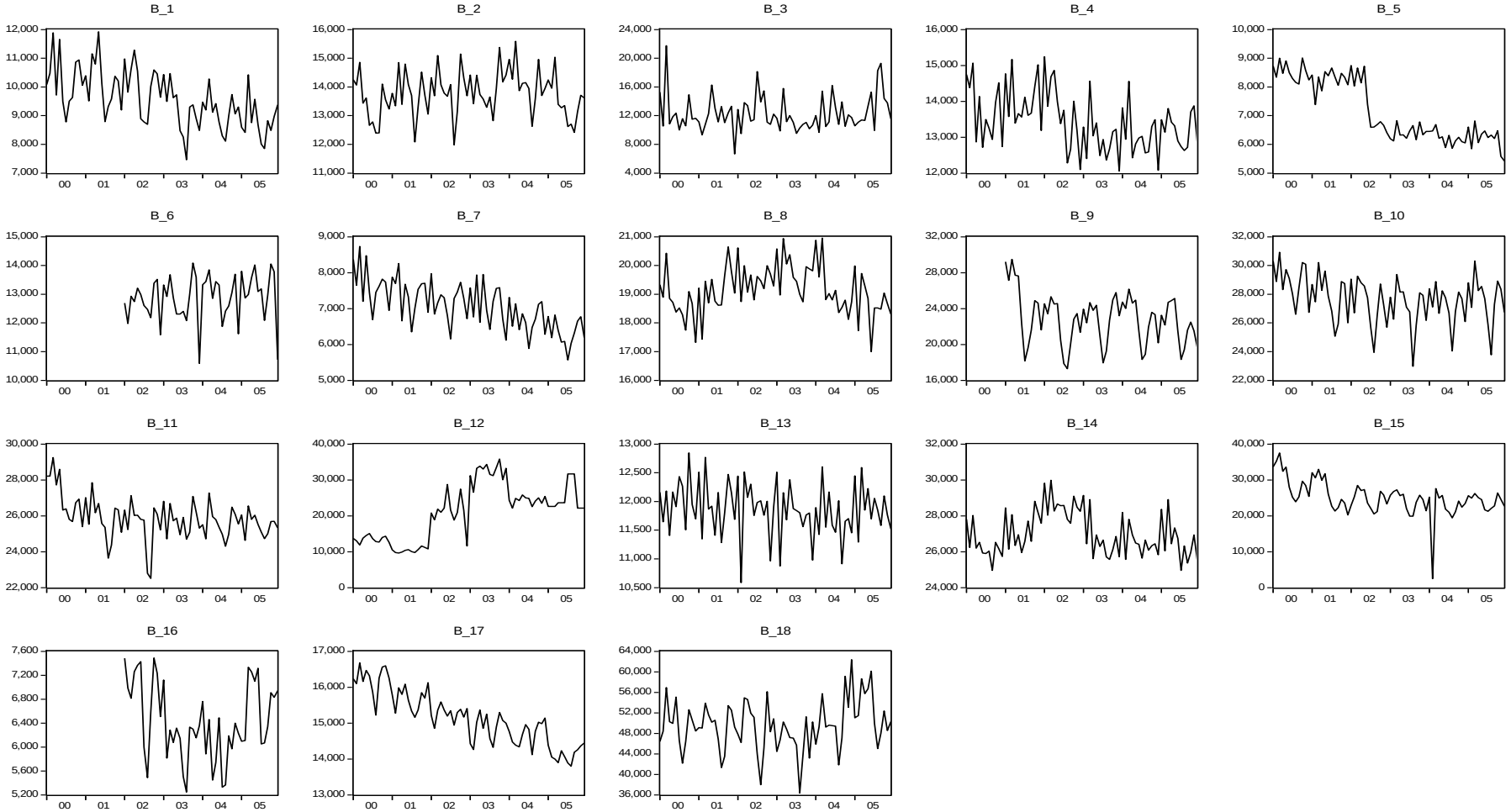


Table A.5.1.3: Plots of admissions or A over time for all hospitals

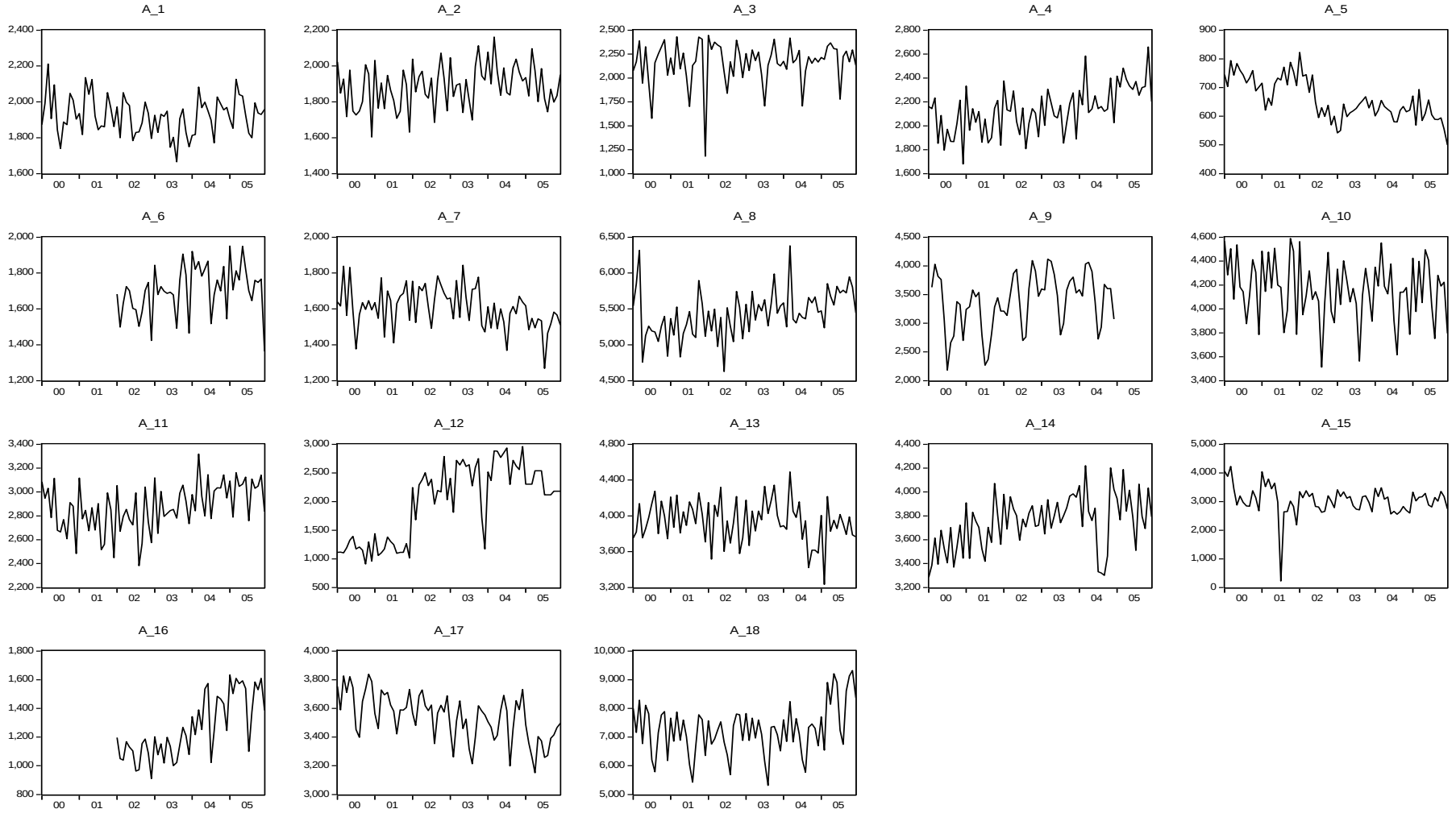


Table A.5.1.4: Plots of lengths of stay or L over time for all hospitals

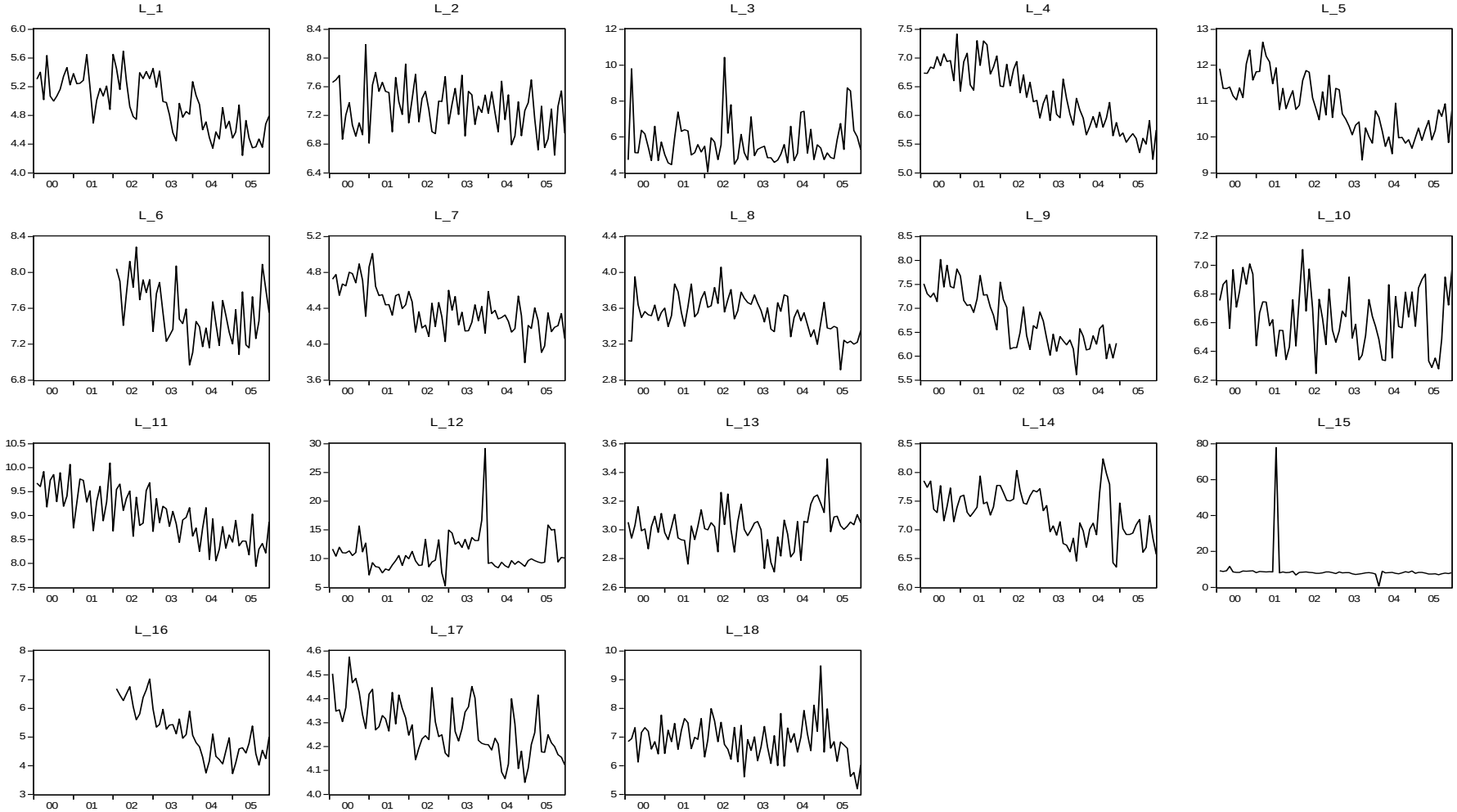
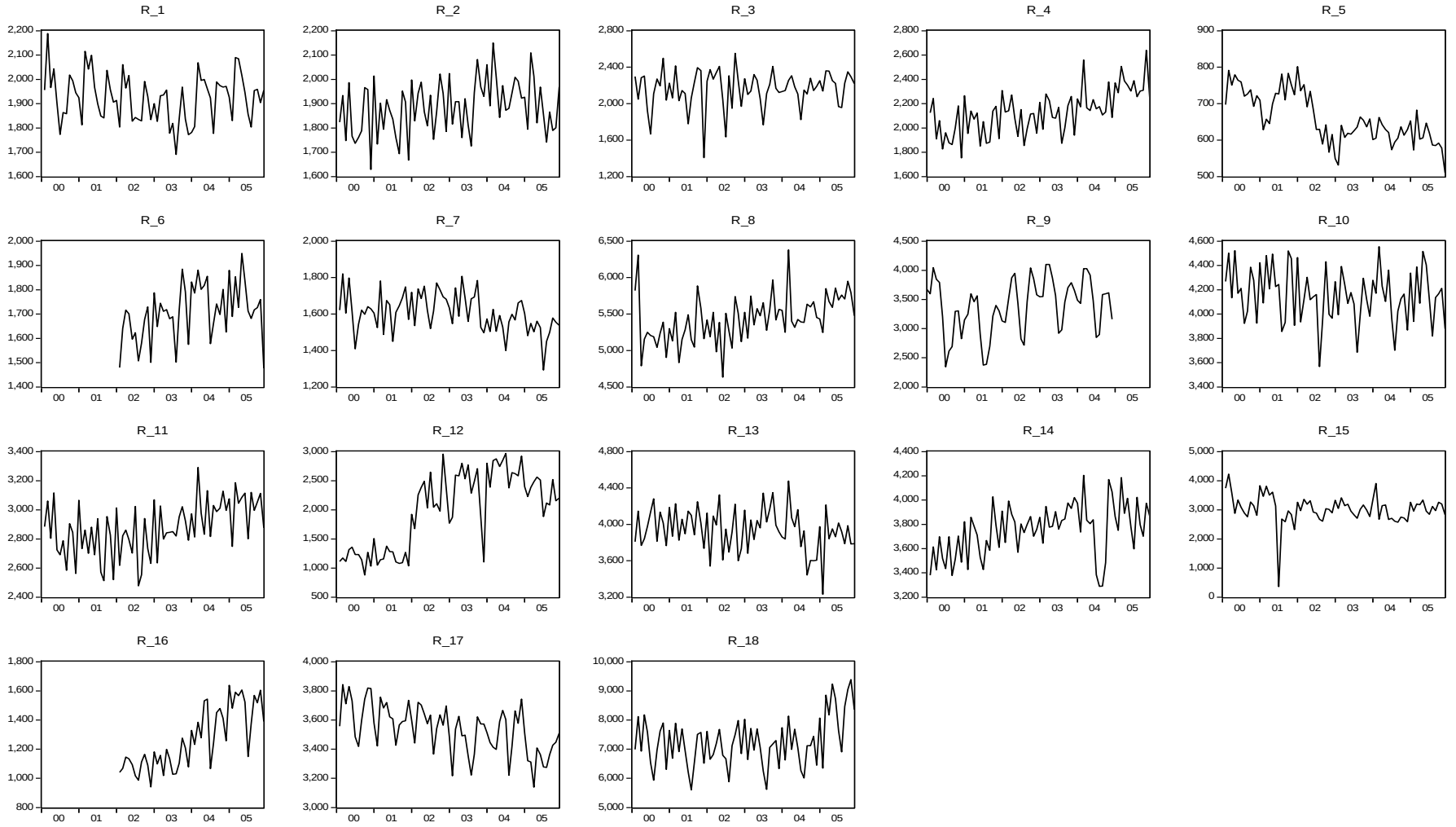


Table A.5.1.5: Plots of discharge or R over time for all hospitals



TableA.5.A. 6: Plots of DDD per occupied bed-days or YPB over time for all hospitals

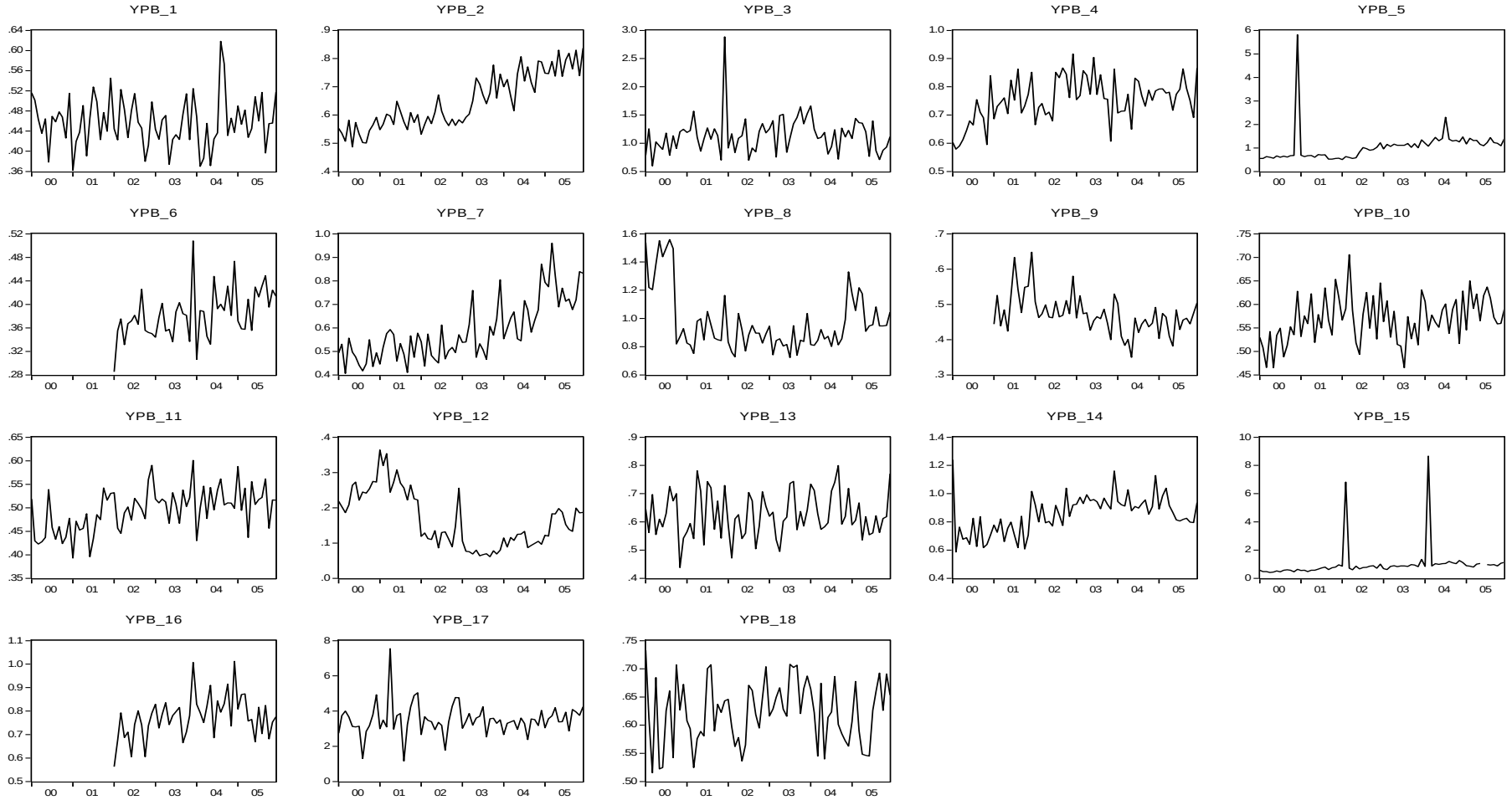


Table A.5.1.7: Plots of DDD per admissions or YBA over time for all hospitals

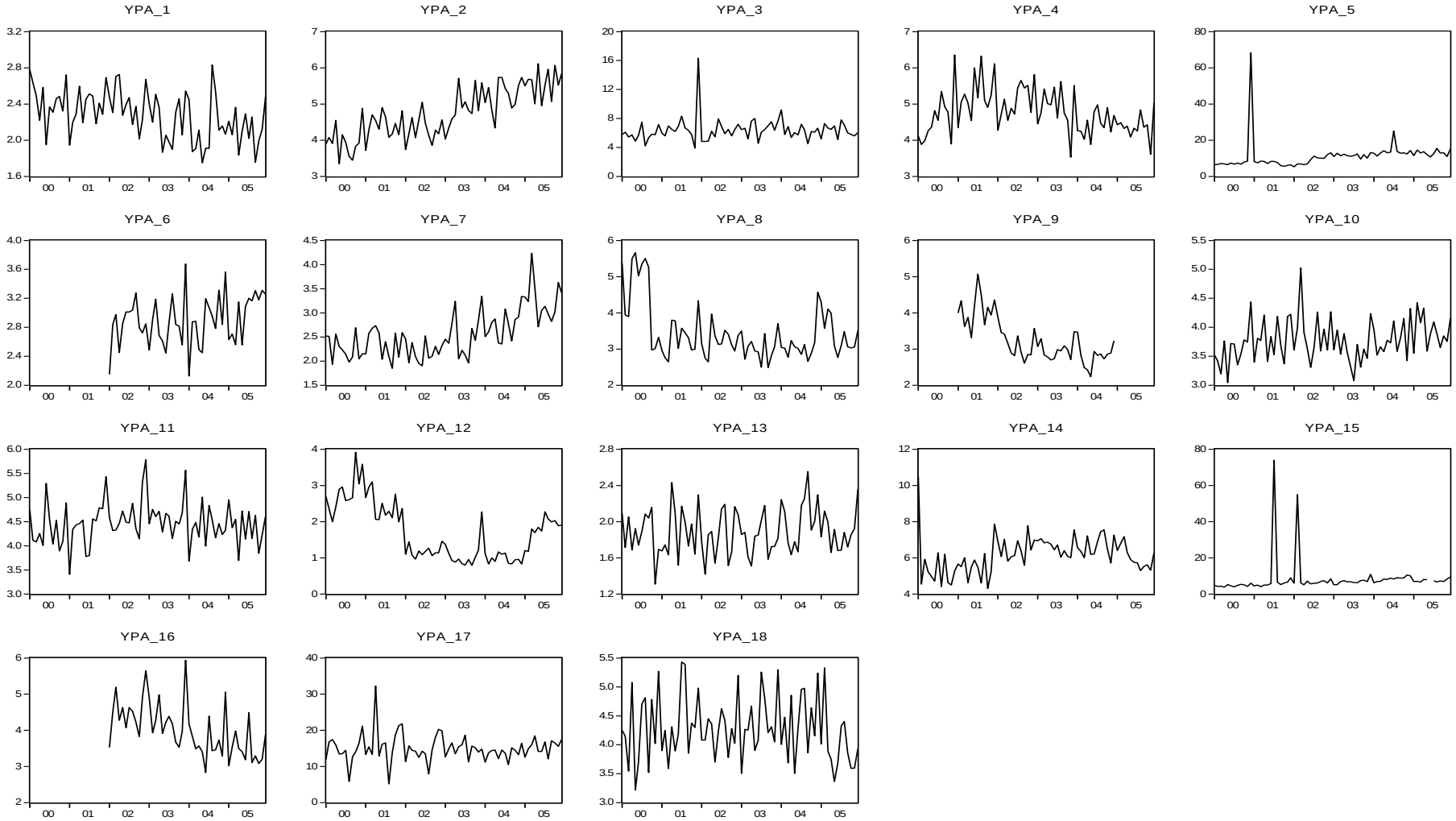


Table A.5.1.8: Plots of antibiotic use in DDD (vertical axis) versus Bed-days (horizontal axis) or YB for all hospitals

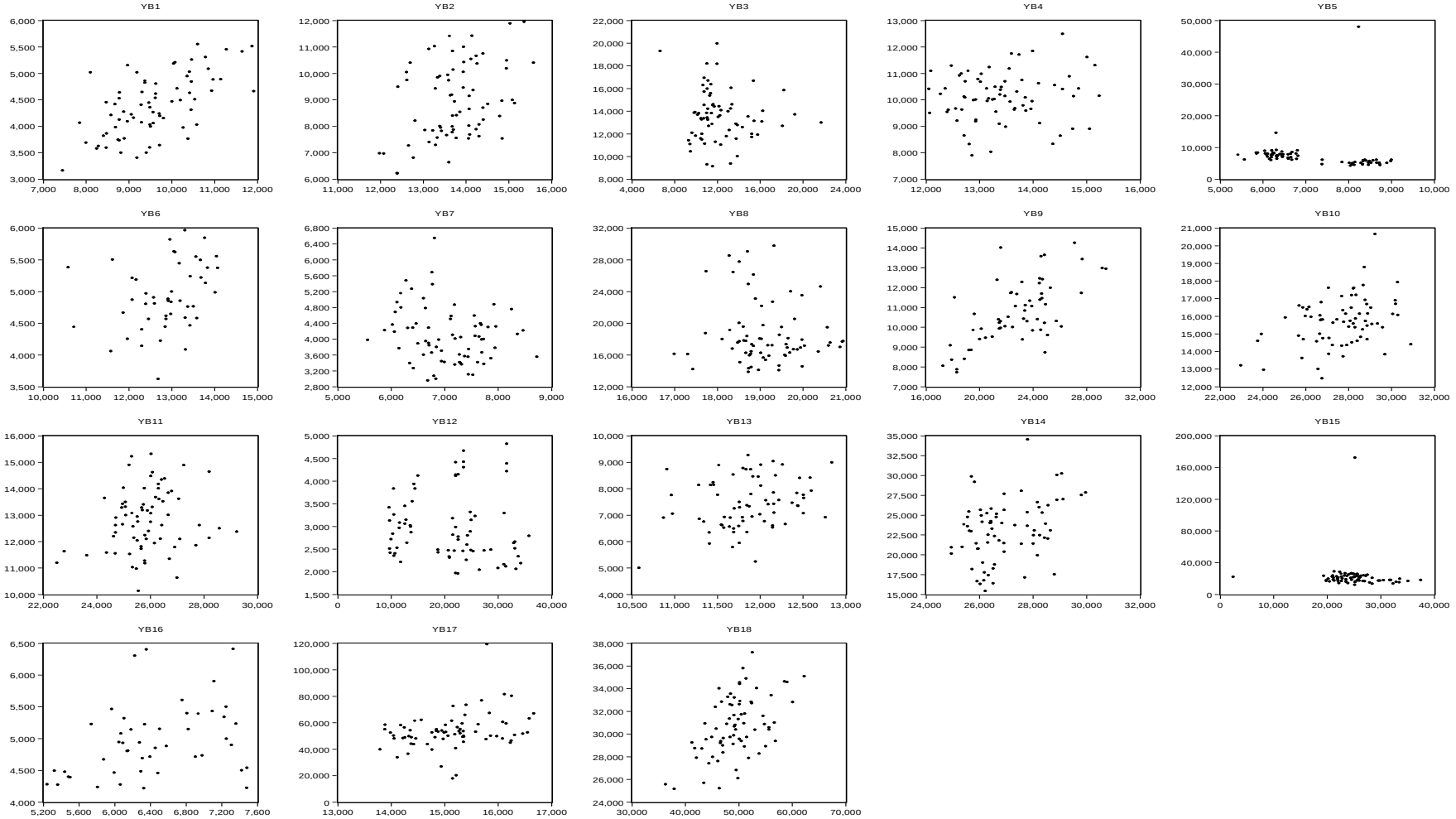


Table A.5.1.9: Plots of antibiotic use in DDD (vertical axis) versus admissions (horizontal axis) or YA for all hospitals

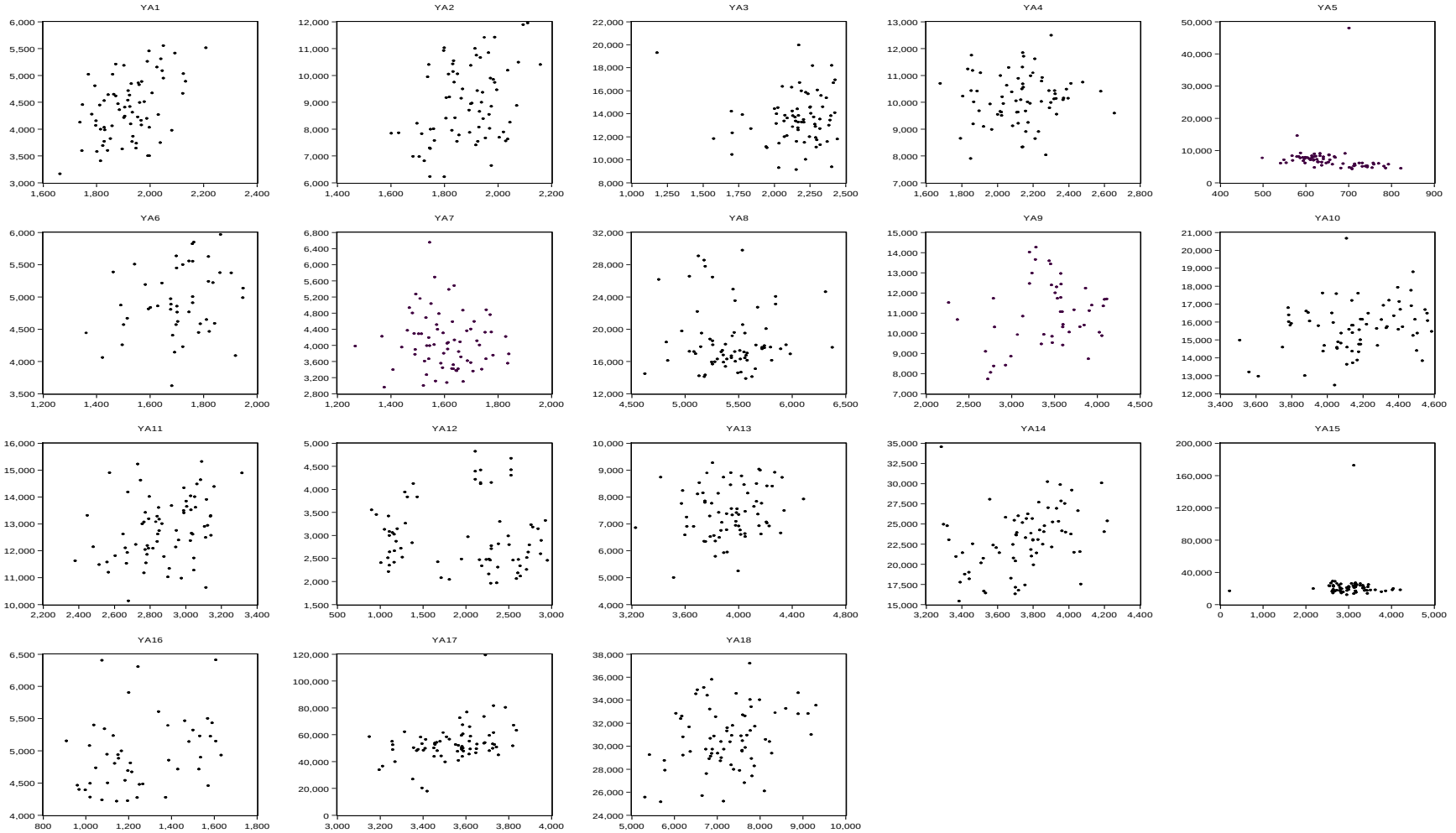
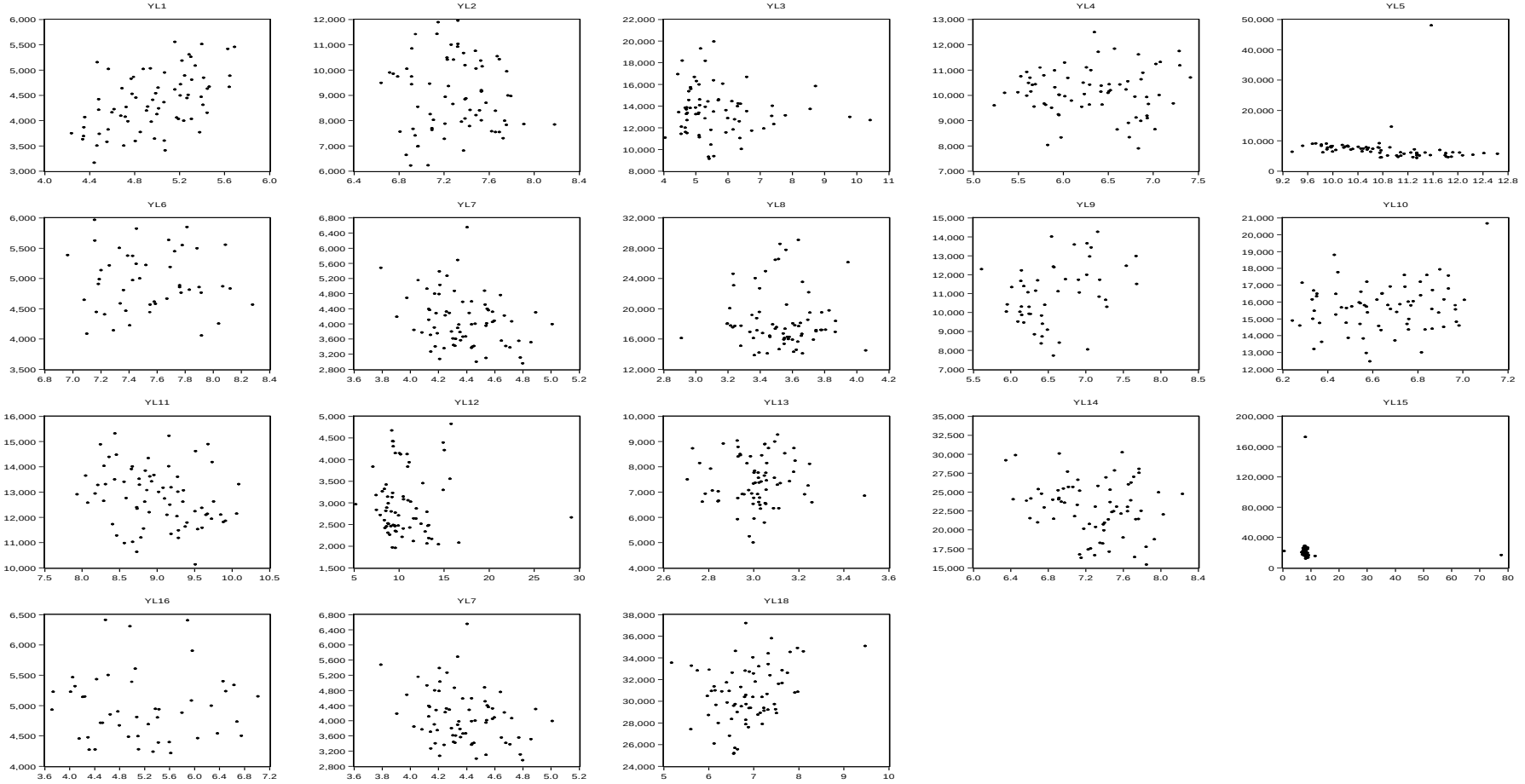


Table A.5.1.10: Plots of antibiotic use in DDD (vertical axis) versus length of stay or YL for all hospitals



Appendix A.5.2 : RESULTS OF THE TIME SERIES REGRESSION ANALYSIS- LONGITUDINAL STUDY ESAC

In all the tables in this appendix, S.E. and S.D. denote standard error and standard deviation, B_G LM Statistic is the Lagrange Multiplier test for residual autocorrelation proposed by Breusch and Godfrey, and Q Statistic is the Ljung-Box Statistic.

1.1. Regression Analysis of the Data from Hospital Number 1

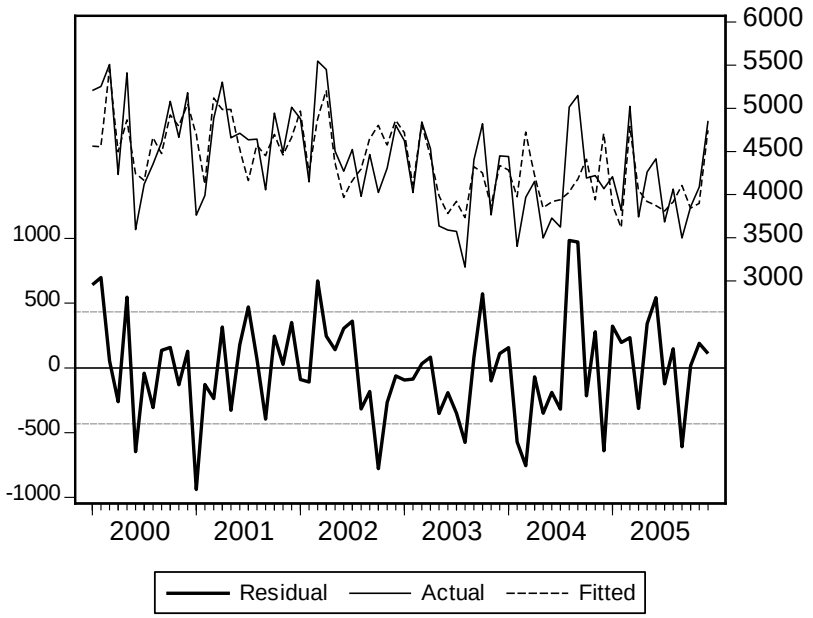
Dependent Variable: Y_t

Sample: 2000M01 2005M12
Included observations: 72

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
B_t	0.454097	0.073442	6.183041	0.0000
Intercept	-17.05715	754.6053	-0.022604	0.9820

R-squared	0.530674	Mean dependent var	4383.243
Adjusted R-squared	0.435218	S.D. dependent var	574.4119
S.E. of regression	431.6818	Akaike info criterion	15.13524
Sum squared resid	10994604	Schwarz criterion	15.54630
B_G LM Statistic:	0.509253;	Prob. F(6,53)	0.798626
Q Statistic	5.0446;	Prob. Chi-Square(6)	0.538

* Seasonal dummies were included but their estimated coefficients of are not reported.



1.2. Regression Analysis of the Data from hospital number 2

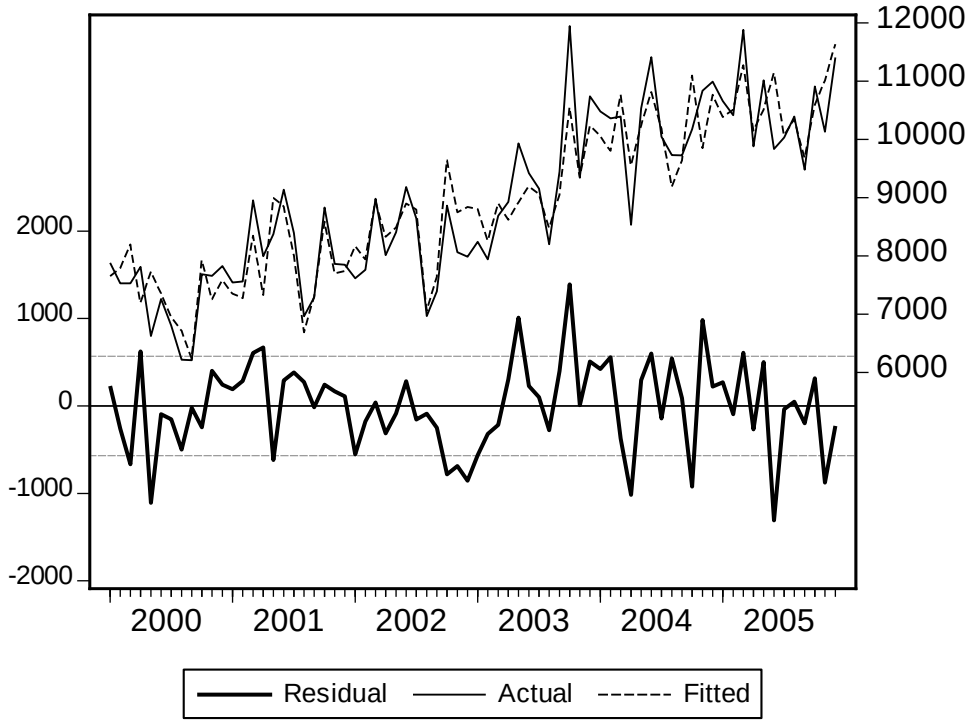
Dependent Variable: Y_t

Sample: 2000M01 2005M12
Included observations: 72

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
B_t	0.900141	0.146592	6.140439	0.0000
Intercept	-5175.403	2112.162	-2.450287	0.0173
t^2	0.734558	0.043365	16.93876	0.0000

R-squared	0.869124	Mean dependent var	8929.465
Adjusted R-squared	0.839790	S.D. dependent var	1419.750
S.E. of regression	568.2720	Akaike info criterion	15.69574
Sum squared resid	18730119	Schwarz criterion	16.13843
B_G LM Statistic:	0.431743;	Prob. F(6,52)	0.854382
Q Statistic	3.4281;	Prob. Chi-Square(6)	0.754

* Seasonal dummies were included but their estimated coefficients of are not reported.



1.3. Regression Analysis of the Data from hospital number 3

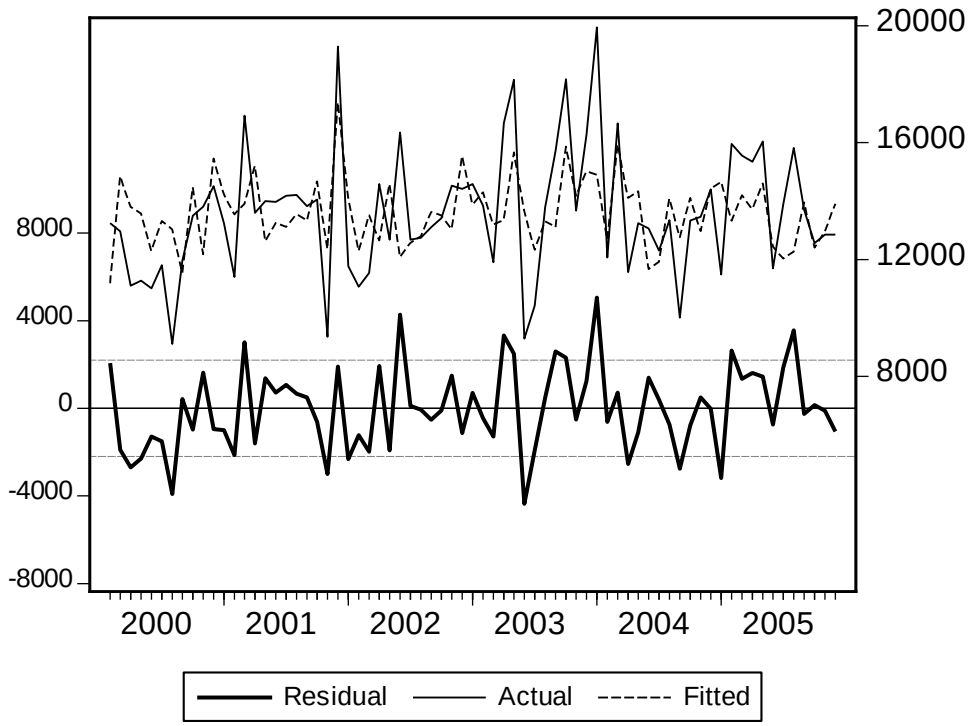
Dependent Variable: Y_t

Sample (adjusted): 2000M02 2005M12
Included observations: 71 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
B_t	-8.165339	3.029973	-2.694855	0.0094
B_{t-1}	7.893086	2.977818	2.650628	0.0105
A_t	242.0226	91.19717	2.653839	0.0104
R_t	-245.2843	91.19520	-2.689662	0.0095
Intercept	24800.99	4827.008	5.137963	0.0000
MA(1)	0.341500	0.149825	2.279327	0.0266

R-squared	0.232054	Mean dependent var	13590.13
Adjusted R-squared	0.004514	S.D. dependent var	2207.099
S.E. of regression	2202.112	Akaike info criterion	18.43740
Sum squared resid	2.62E+08	Schwarz criterion	18.97917
B_G LM Statistic:	0.531749;	Prob. F(6,48)	0.781388
Q Statistic	2.2957;	Prob. Chi-Square(6)	0.807

* Seasonal dummies were included but their estimated coefficients of are not reported. MA(1) captures the residual dynamics.



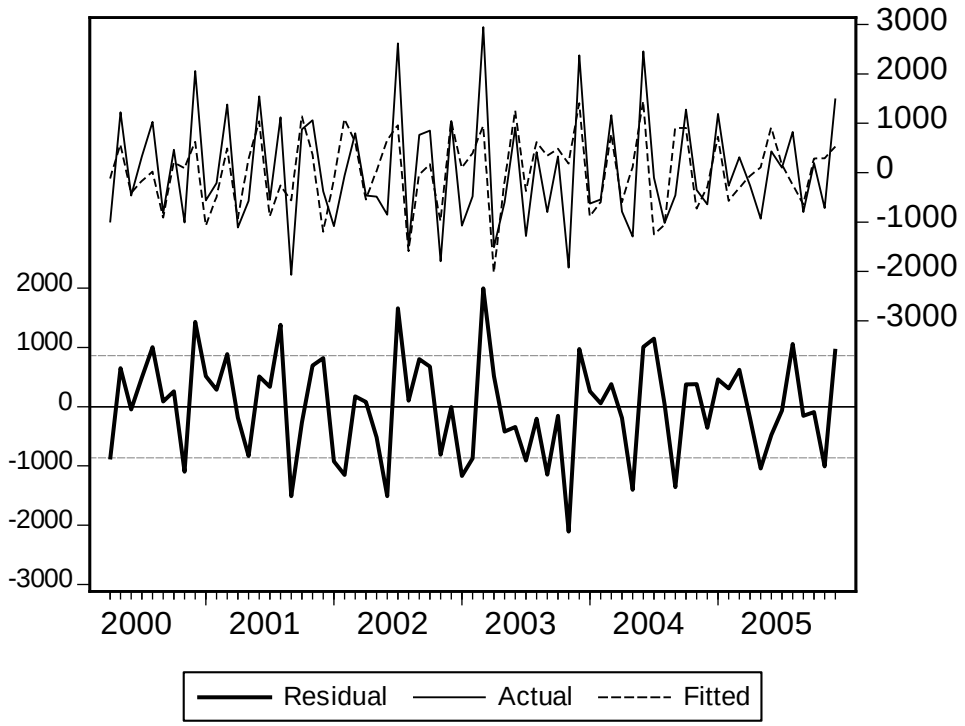
1.4. Regression Analysis of the Data from hospital number 4

Dependent Variable: ΔY_t

Sample (adjusted): 2000M04 2005M12
Included observations: 69 after adjustments

Variable	Coefficient	Std. Error	t-Statistic	Prob.
ΔY_{t-1}	-0.785096	0.109130	-7.194099	0.0000
ΔY_{t-2}	-0.482277	0.109252	-4.414371	0.0000
Intercept	55.87122	103.8089	0.538212	0.5922

R-squared	0.442214	Mean dependent var.	31.73176
Adjusted R-squared	0.425311	S.D. dependent var.	1136.762
S.E. of regression	861.7593	Akaike info criterion	16.39833
Sum squared residuals	49013524	Schwarz criterion	16.49547
B_G LM Statistic:	1.003410;	Prob. F(6,60)	0.431659
Q Statistic	5.0446;	Prob. Chi-Square(6)	0.538



1.5. Regression Analysis of the Data from hospital number 5

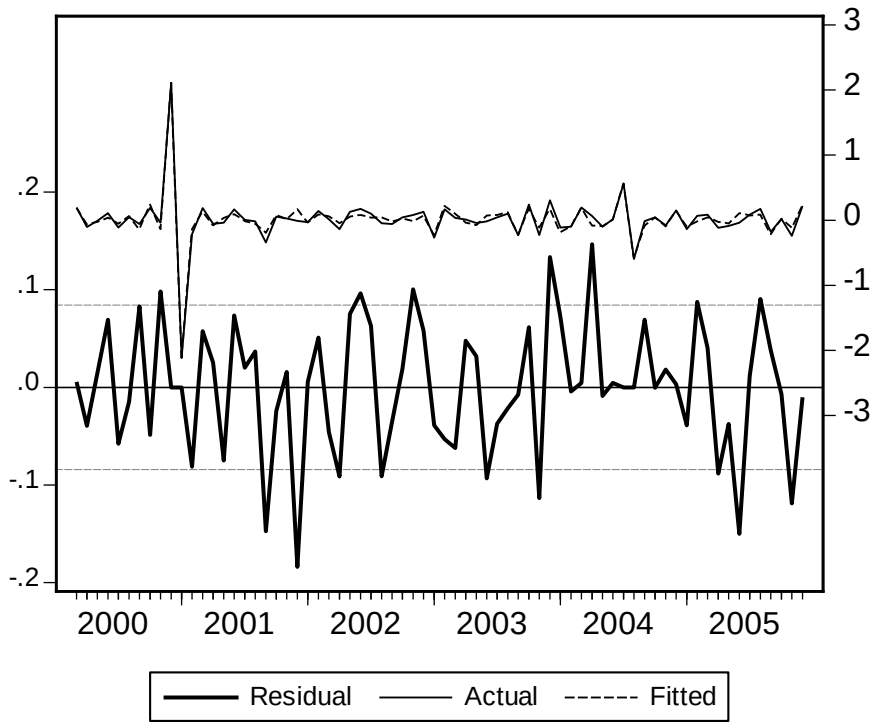
Dependent Variable: $\Delta \ln Y_t$

Sample (adjusted): 2000M03 2005M12
Included observations: 70 after adjustments

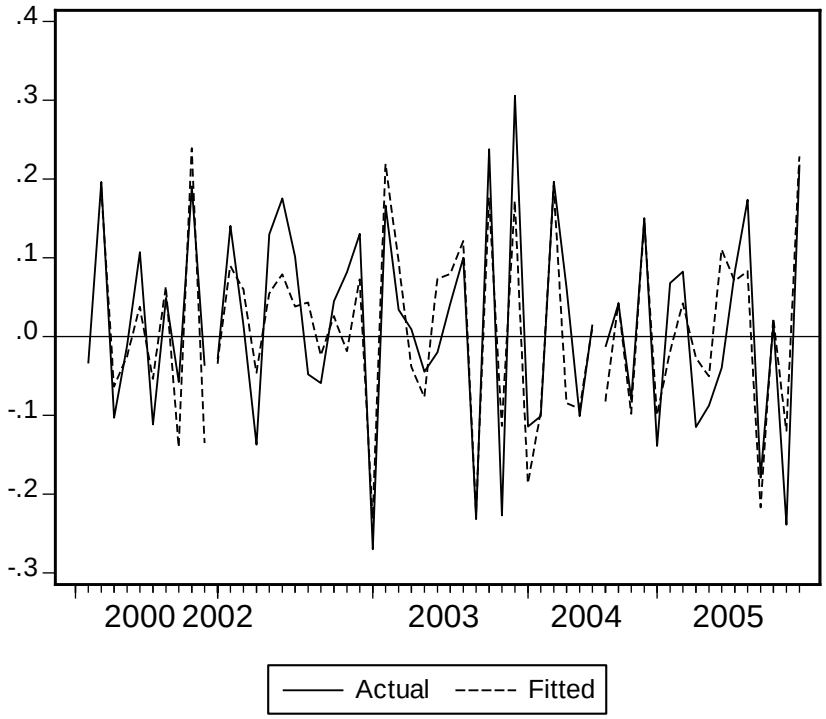
Variable*	Coefficient	Std. Error	t-Statistic	Prob.
$\Delta \ln B_t$	707.2610	210.6873	3.356923	0.0016
$\Delta \ln A_t$	-341.7690	104.0279	-3.285358	0.0020
$\Delta \ln R_t$	-369.3104	107.2161	-3.444542	0.0012
$\Delta \ln L_t$	-710.7488	211.0320	-3.367967	0.0016
$\ln Y_{t-1}$	-0.321629	0.126308	-2.546390	0.0144
$\ln B_{t-1}$	865.1927	283.0196	3.057006	0.0038
$\ln A_{t-1}$	-417.2828	139.8754	-2.983248	0.0046
$\ln R_{t-1}$	-448.2346	143.2149	-3.129804	0.0031
$\ln L_{t-1}$	-865.8163	283.0070	-3.059346	0.0037
Intercept	6.238129	2.766990	2.254482	0.0291

R-squared	0.970454	Mean dependent var	0.006987
Adjusted R-squared	0.954697	S.D. dependent var	0.395346
S.E. of regression	0.084148	Akaike info criterion	-1.840035
Sum squared resid	0.318637	Schwarz criterion	-1.037001
B_G LM Statistic:	1.027840;	Prob. F(6,39)	0.421995
Q Statistic	5.4606;	Prob. Chi-Square(6)	0.486

* Seasonal and shift dummies were included but their estimated coefficients of are not reported.



Given the existence of outlier, the above graph does not show the tracking power of the model. We therefore plot below the actual and fitted values in a graph that excludes the outliers hence giving a better description due to scale correction.



1.6. Regression Analysis of the Data from Hospital number 6

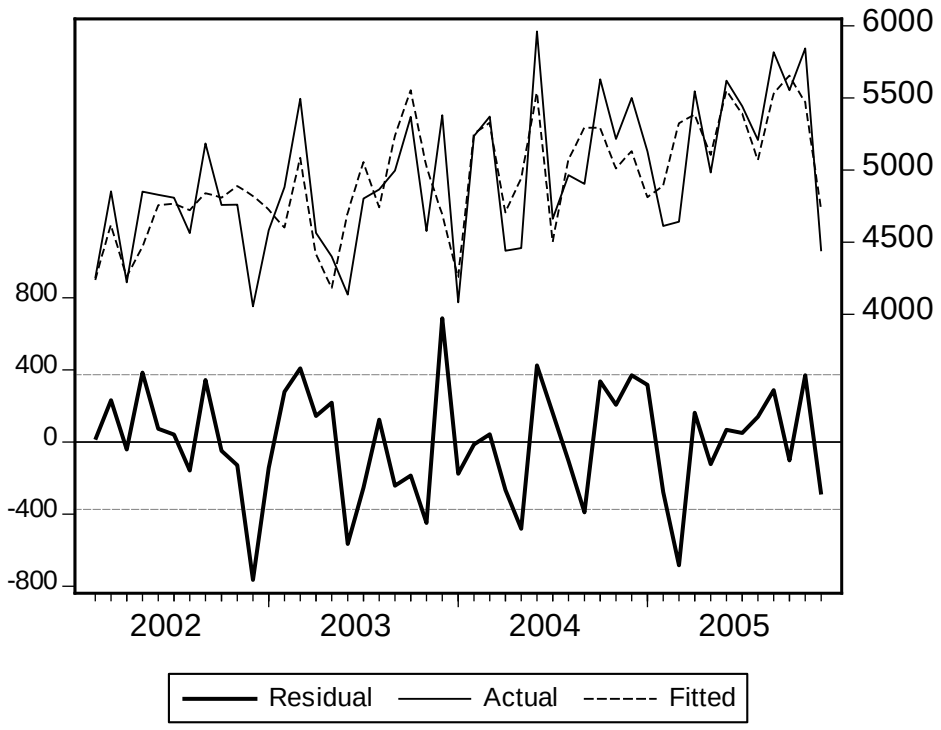
Dependent Variable: Y_t

Sample (adjusted): 2002M02 2005M12
Included observations: 47 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
B_t	0.435899	0.126870	3.435800	0.0017
Intercept	-1868.037	1672.381	-1.116993	0.2723
t	13.27332	3.305054	4.016069	0.0003
AR(1)	-0.394561	0.166935	-2.363559	0.0243

R-squared	0.600637	Mean dependent var	4945.737
Adjusted R-squared	0.425915	S.D. dependent var	493.6625
S.E. of regression	374.0401	Akaike info criterion	14.94049
Sum squared resid	4476993.	Schwarz criterion	15.53096
B_G LM Statistic:	0.736728;	Prob. F(6,26)	0.624746
Q Statistic	5.8763;	Prob. Chi-Square(6)	0.318

* Seasonal dummies were included but their estimated coefficients of are not reported. AR(1) captures the residual dynamics.



1.7. Regression Analysis of the Data from hospital number 7

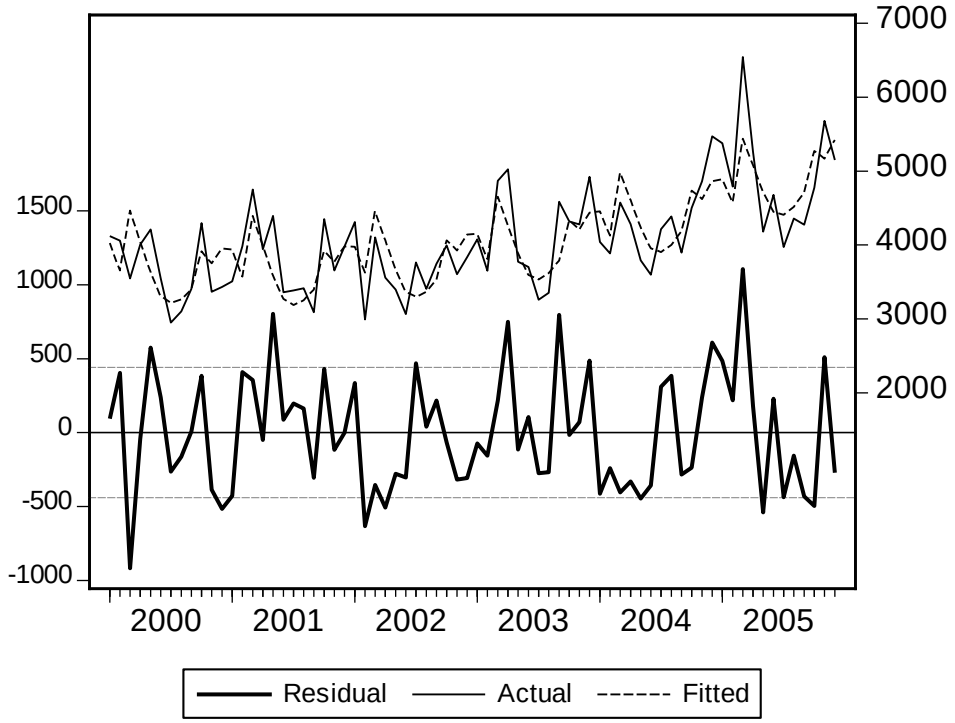
Dependent Variable: Y_t

Sample: 2000M01 2005M12
Included observations: 72

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
Intercept	4040.993	229.5136	17.60677	0.0000
t	-14.01800	10.14780	-1.381382	0.1725
t^2	0.458597	0.134602	3.407068	0.0012

R-squared	0.666854	Mean dependent var	4083.272
Adjusted R-squared	0.592183	S.D. dependent var	690.4637
S.E. of regression	440.9340	Akaike info criterion	15.18833
Sum squared resid	11276520	Schwarz criterion	15.63102
B_G LM Statistic:	1.497529;	Prob. F(6,52)	0.197434
Q Statistic	7.6273;	Prob. Chi-Square(6)	0.267

* Seasonal dummies were included but their estimated coefficients of are not reported.



1.8. Regression Analysis of the Data from hospital number 8

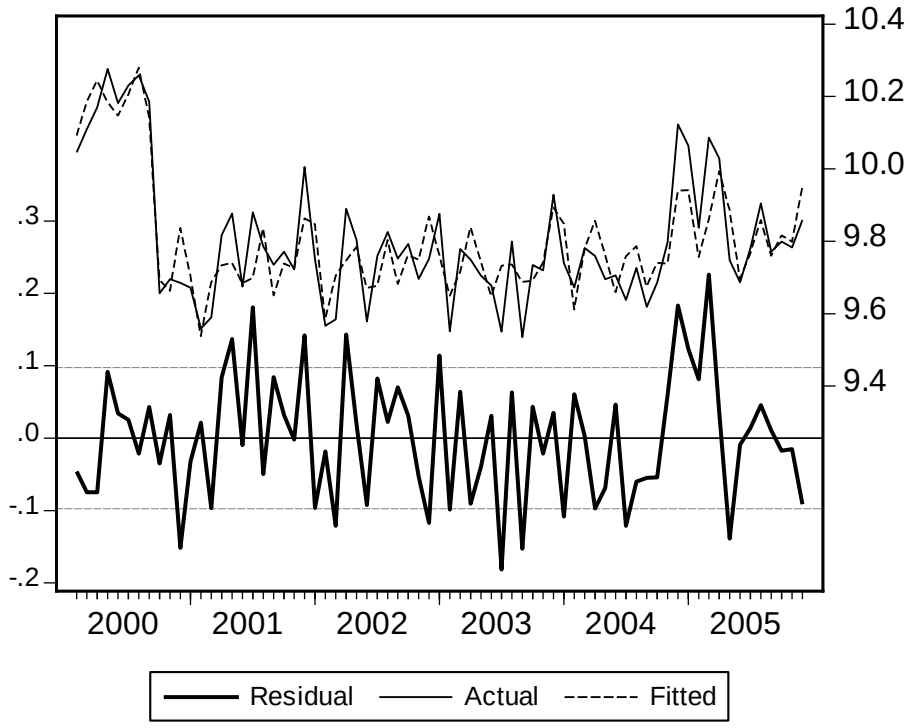
Dependent Variable: $\ln Y_t$

Sample (adjusted): 2000M02 2005M12
Included observations: 71 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
Intercept	9.732511	0.063513	153.2362	0.0000
t	0.002168	0.001085	1.997832	0.0506
AR(1)	0.397041	0.124081	3.199865	0.0023

R-squared	0.772537	Mean dependent var	9.806051
Adjusted R-squared	0.715671	S.D. dependent var	0.183088
S.E. of regression	0.097627	Akaike info criterion	-1.630118
Sum squared resid	0.533738	Schwarz criterion	-1.152087
B_G LM Statistic:	0.784650;	Prob. F(6,50)	0.586045
Q Statistic	5.2926;	Prob. Chi-Square(6)	0.381

* Seasonal and shift dummies were included but their estimated coefficients of are not reported. AR(1) captures the residual dynamics.



1.9. Regression Analysis of the Data from hospital number 9

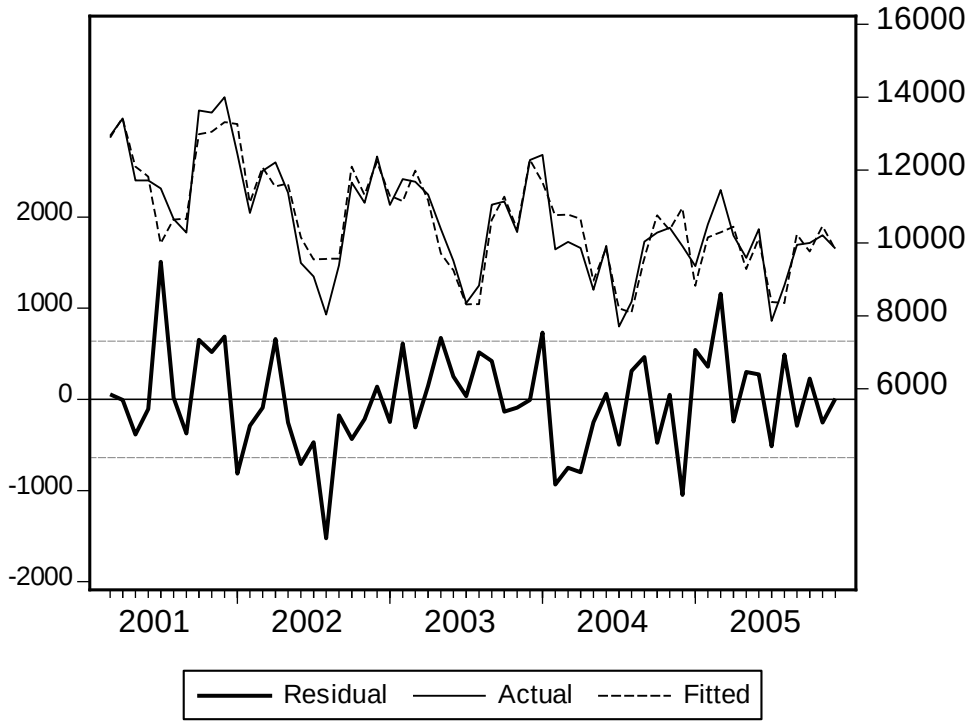
Dependent Variable: Y_t

Sample (adjusted): 2001M03 2005M12
Included observations: 58 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
B_{t-1}	0.736599	0.087365	8.431303	0.0000
A_{t-1}	-2.850515	0.415266	-6.864316	0.0000
Intercept	4354.114	1480.002	2.941965	0.0051
AR(1)	-0.597508	0.131400	-4.547257	0.0000
MA(1)	0.973618	0.027295	35.66990	0.0000

R-squared	0.822281	Mean dependent var	10592.42
Adjusted R-squared	0.778838	S.D. dependent var	1465.603
S.E. of regression	689.2414	Akaike info criterion	16.09372
Sum squared resid	21377415	Schwarz criterion	16.52384
B_G LM Statistic:	1.056644;	Prob. F(6,36)	0.4048
Q Statistic	62480;	Prob. Chi-Square(6)	0.181

* Seasonal dummies were included but their estimated coefficients of are not reported. AR(1) and MA(1) capture the residual dynamics.



1.10. Regression Analysis of the Data from hospital number 10

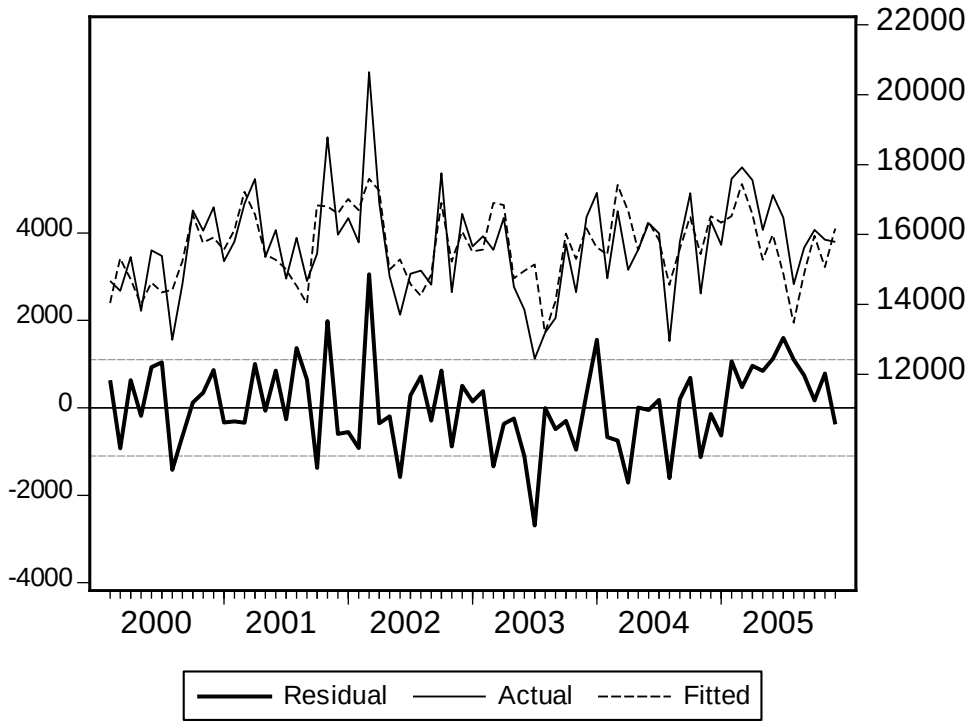
Dependent Variable: Y_t

Sample (adjusted): 2000M02 2005M12
Included observations: 71 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
Y_{t-1}	0.844921	0.042662	19.80500	0.0000
B_t	-4.274486	1.536348	-2.782238	0.0074
A_t	29.59793	10.23078	2.893026	0.0055
L_t	17917.15	6423.370	2.789369	0.0073
Intercept	-123283.0	42834.48	-2.878126	0.0057
MA(1)	-0.983601	0.018640	-52.76690	0.0000

R-squared	0.523325	Mean dependent var	15672.07
Adjusted R-squared	0.382088	S.D. dependent var	1403.604
S.E. of regression	1103.336	Akaike info criterion	17.05524
Sum squared resid	65736948	Schwarz criterion	17.59701
B_G LM Statistic:	1.429524;	Prob. F(6,48)	0.223027
Q Statistic	9.3034;	Prob. Chi-Square(6)	0.098

* Seasonal dummies were included but their estimated coefficients of are not reported. MA(1) captures the residual dynamics.



1.11. Regression Analysis of the Data from hospital number 11

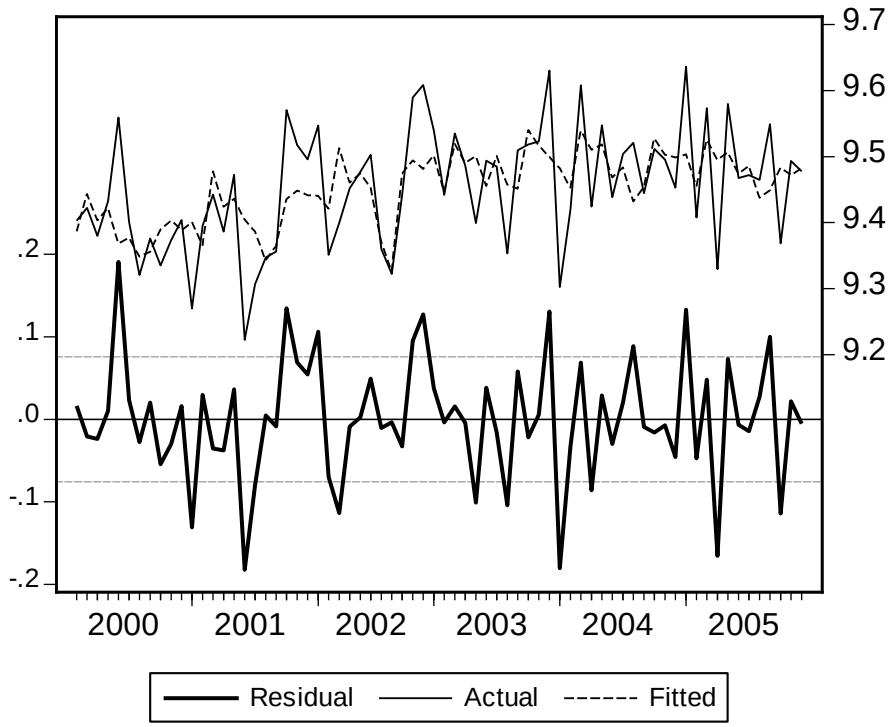
Dependent Variable: $\ln Y_t$

Sample (adjusted): 2000M02 2005M12
Included observations: 71 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
$\ln R_t$	0.980834	0.242254	4.048779	0.0001
$\ln L_t$	1.193358	0.343932	3.469755	0.0009
Intercept	-1.152078	2.555076	-0.450898	0.6536
t	0.008016	0.002073	3.866234	0.0003
t^2	-6.90E-05	2.57E-05	-2.689738	0.0091

R-squared	0.922550	Mean dependent var	9.422892
Adjusted R-squared	0.916592	S.D. dependent var	0.261721
S.E. of regression	0.075586	Akaike info criterion	-2.246367
Sum squared resid	0.371362	Schwarz criterion	-2.055154
B_G LM Statistic:	1.362161;	Prob. F(6,59)	0.244914
Q Statistic	7.2599;	Prob. Chi-Square(6)	0.297

* A shit dummy was included but its estimated coefficient of is not reported.



1.12. Regression Analysis of the Data from Hospital Number 12

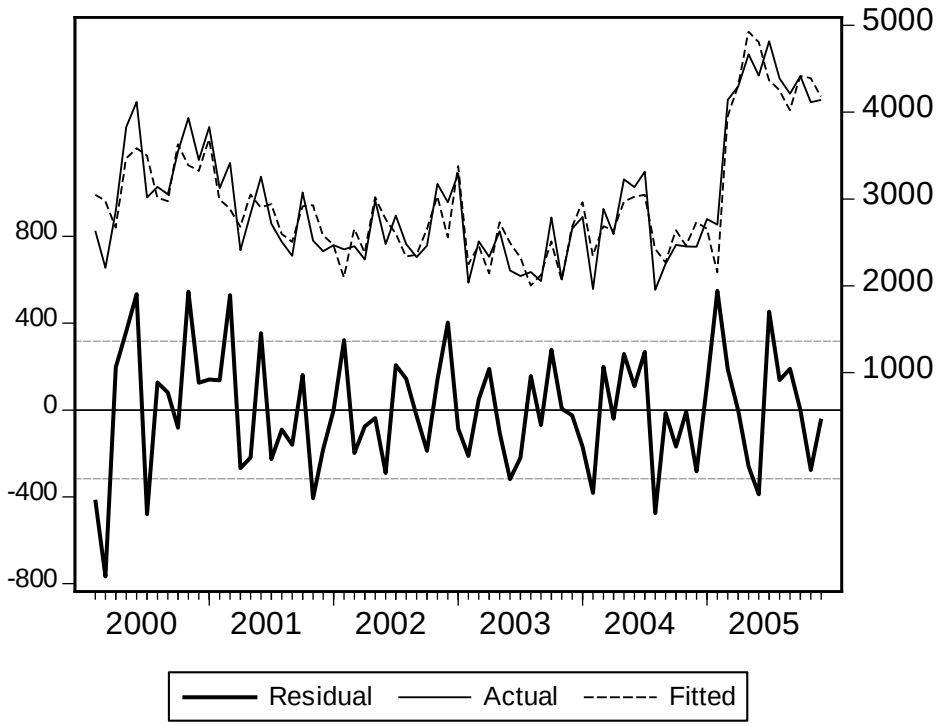
Dependent Variable: Y_t

Sample (adjusted): 2000M02 2005M12
Included observations: 71 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
Y_{t-1}	0.340986	0.102936	3.312595	0.0017
B_t	-0.094158	0.024329	-3.870202	0.0003
A_t	1.571175	0.333532	4.710711	0.0000
L_t	168.7663	40.63591	4.153131	0.0001
Intercept	-519.3450	784.5208	-0.661990	0.5110
t	-12.80094	5.190120	-2.466405	0.0170

R-squared	0.866824	Mean dependent var	2971.050
Adjusted R-squared	0.817210	S.D. dependent var	741.9428
S.E. of regression	317.2098	Akaike info criterion	14.58953
Sum squared resid	5131724.	Schwarz criterion	15.22690
B_G LM Statistic:	0.843580;	Prob. F(6,45)	0.543200
Q Statistic	5.8840;	Prob. Chi-Square(6)	0.436

* Seasonal dummies were included but their estimated coefficients of are not reported.



1.13. Regression Analysis of the Data from Number 13

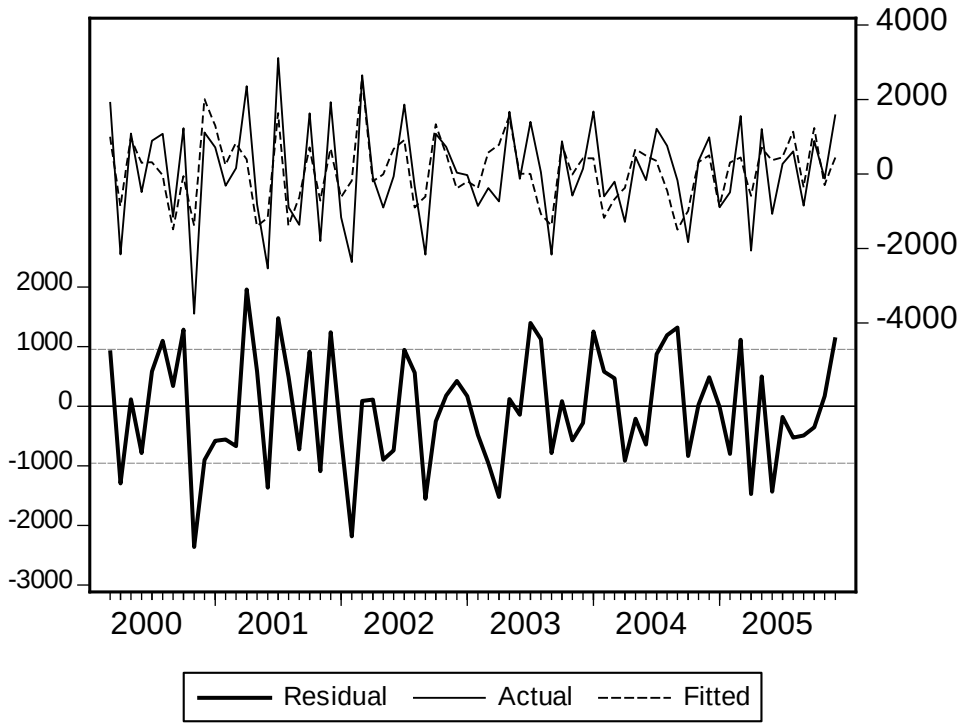
Dependent Variable: ΔY_t

Sample (adjusted): 2000M03 2005M12
Included observations: 70 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
ΔY_{t-1}	-0.864653	0.063405	-13.63698	0.0000
Intercept	0.537762	12.40801	0.043340	0.9656
MA(2)	-0.955491	0.029020	-32.92502	0.0000

R-squared	0.521507	Mean dependent var	33.27455
Adjusted R-squared	0.507224	S.D. dependent var	1364.617
S.E. of regression	957.9340	Akaike info criterion	16.60935
Sum squared resid	61481714	Schwarz criterion	16.70571
B_G LM Statistic:	0.785024;	Prob. F(6,61)	0.585011
Q Statistic	3.8918;	Prob. Chi-Square(6)	0.565

* MA(2) capture the residual dynamics.



1.14. Regression Analysis of the Data from Hospital Number 14

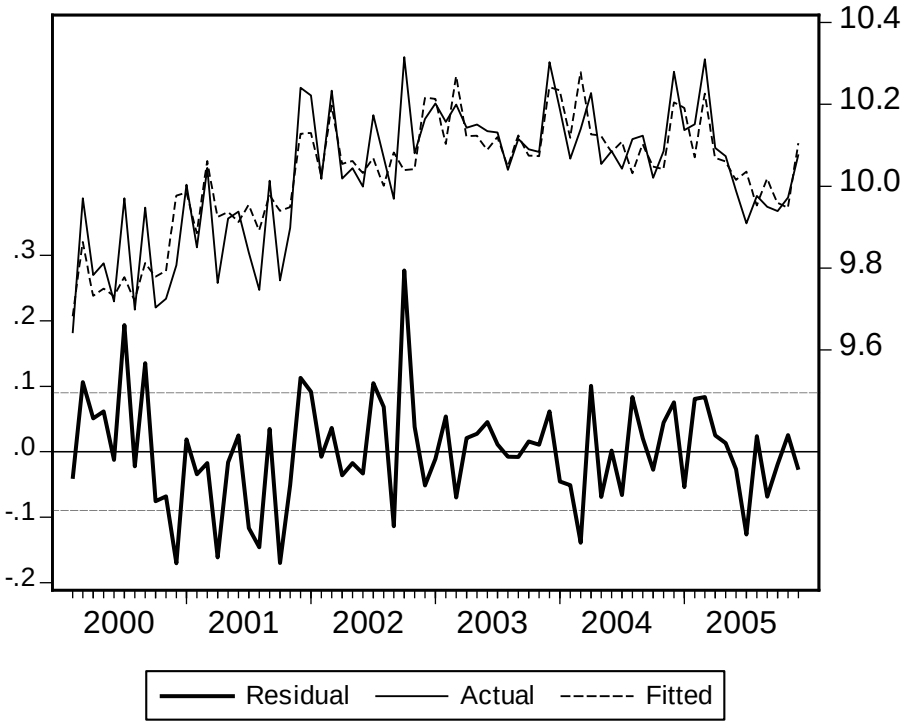
Dependent Variable: $\ln Y_t$

Sample: 2000M02 2005M12
Included observations: 71

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
Intercept	9.756242	0.054386	179.3880	0.0000
t	0.020397	0.002181	9.352617	0.0000
t^2	-0.000217	2.86E-05	-7.603508	0.0000

R-squared	0.748229	Mean dependent var	10.02630
Adjusted R-squared	0.690808	S.D. dependent var	0.161935
S.E. of regression	0.090044	Akaike info criterion	-1.802293
Sum squared resid	0.462154	Schwarz criterion	-1.356131
B_G LM Statistic:	1.240879;	Prob. F(6,51)	0.301374
Q Statistic	10.723;	Prob. Chi-Square(6)	0.097

* Seasonal dummies were included but their estimated coefficients of are not reported.



1.15. Regression Analysis of the Data from hospital number 15

Dependent Variable: $\Delta \ln Y_t$

Sample (adjusted): 2000M03 2005M12

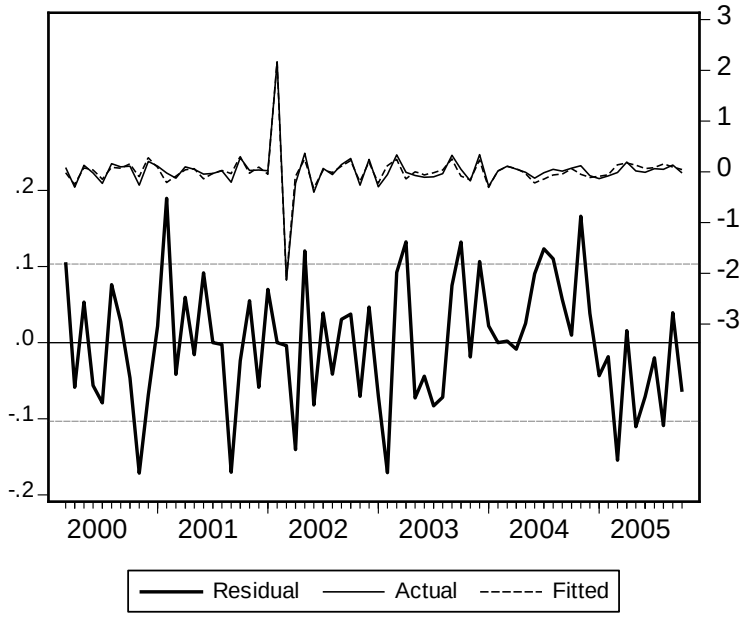
Included observations: 68 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
$\Delta \ln B_t$	499.6413	238.6771	2.093377	0.0422
$\Delta \ln A_t$	-239.9044	114.7637	-2.090420	0.0425
$\Delta \ln R_t$	-262.5544	125.4771	-2.092448	0.0423
$\Delta \ln L_t$	-502.9137	240.1492	-2.094172	0.0422
$\ln Y_{t-1}$	-0.969470	0.050355	-19.25274	0.0000
$\ln B_{t-1}$	483.4159	239.3514	2.019691	0.0497
$\ln A_{t-1}$	-229.6148	114.2738	-2.009339	0.0508
$\ln R_{t-1}$	-254.1200	125.1285	-2.030873	0.0485
$\ln L_{t-1}$	-483.7197	239.3273	-2.021164	0.0495
Intercept	12.42662	2.377864	5.225958	0.0000
t	0.007070	0.001116	6.336308	0.0000

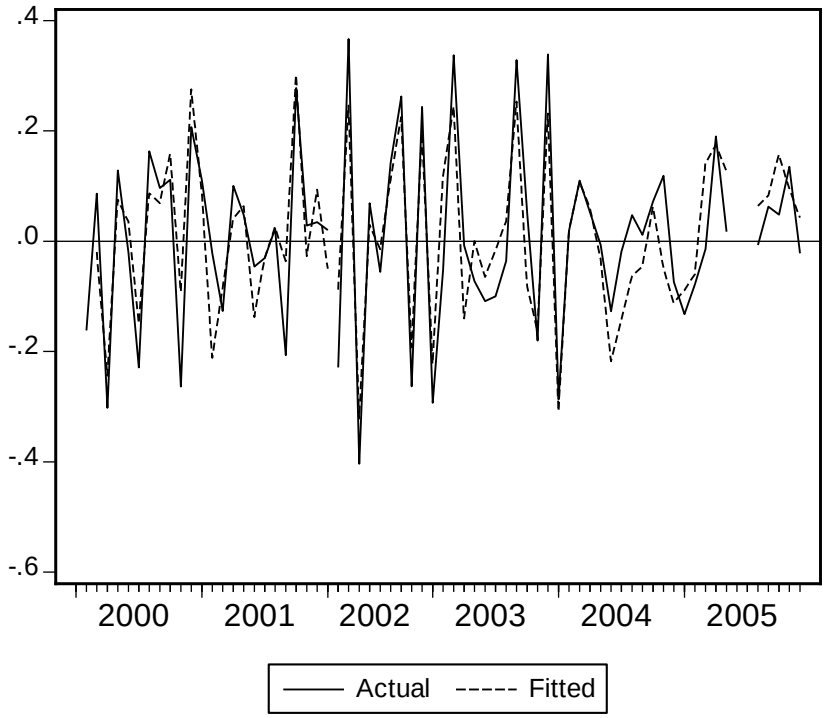
R-squared	0.958252	Mean dependent var	0.009821
Adjusted R-squared	0.934950	S.D. dependent var	0.405571
S.E. of regression	0.103441	Akaike info criterion	-1.422653
Sum squared resid	0.460098	Schwarz criterion	-0.606657

B_G LM Statistic:	0.134798;	Prob. F(6,37)	0.990885
Q Statistic	1.7127;	Prob. Chi-Square(6)	0.944

* Seasonal and shit dummies were included but their estimated coefficients of are not reported.



Given the existence of outlier, the above graph does not show the tracking power of the model. We therefore plot below the actual and fitted values in a graph that excludes the outliers hence giving a better description due to scale correction.



1.16. Regression Analysis of the Data from Hospital Number 16

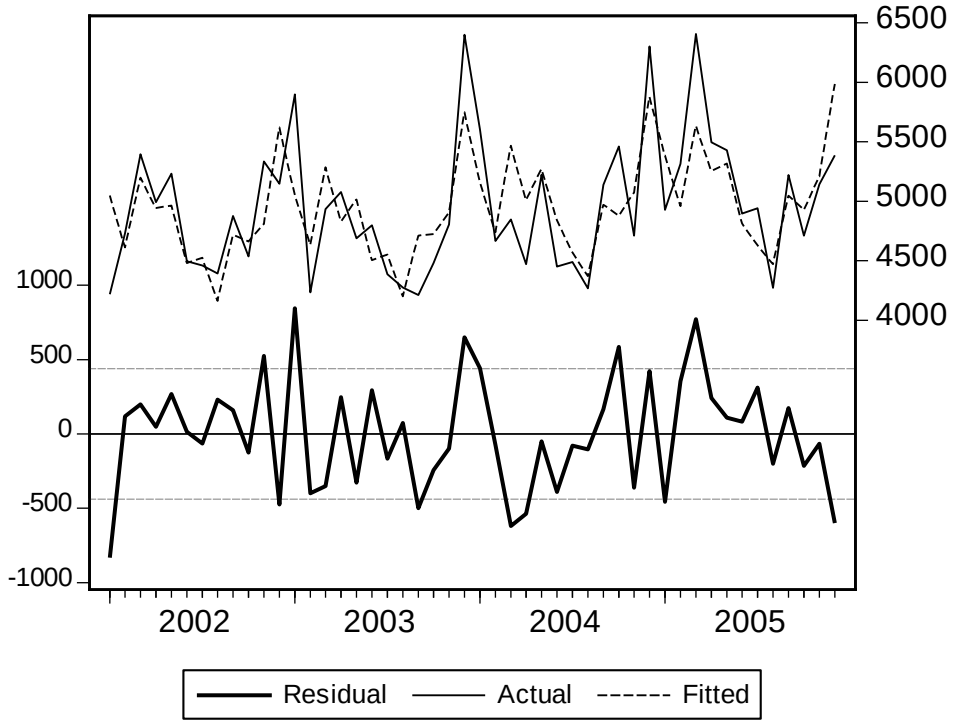
Dependent Variable: Y_t

Sample (adjusted): 2002M01 2005M12
Included observations: 48 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
A_t	0.767332	0.346870	2.212162	0.0336
Intercept	4130.653	515.2639	8.016577	0.0000

R-squared	0.540628	Mean dependent var	4953.610
Adjusted R-squared	0.383129	S.D. dependent var	559.3012
S.E. of regression	439.2815	Akaike info criterion	15.23397
Sum squared resid	6753888.	Schwarz criterion	15.74076
B_G LM Statistic:	0.563875;	Prob. F(6,29)	0.755384
Q Statistic	5.2975;	Prob. Chi-Square(6)	0.506

* Seasonal dummies were included but their estimated coefficients of are not reported.



1.17 Regression Analysis of the Data from hospital number 17

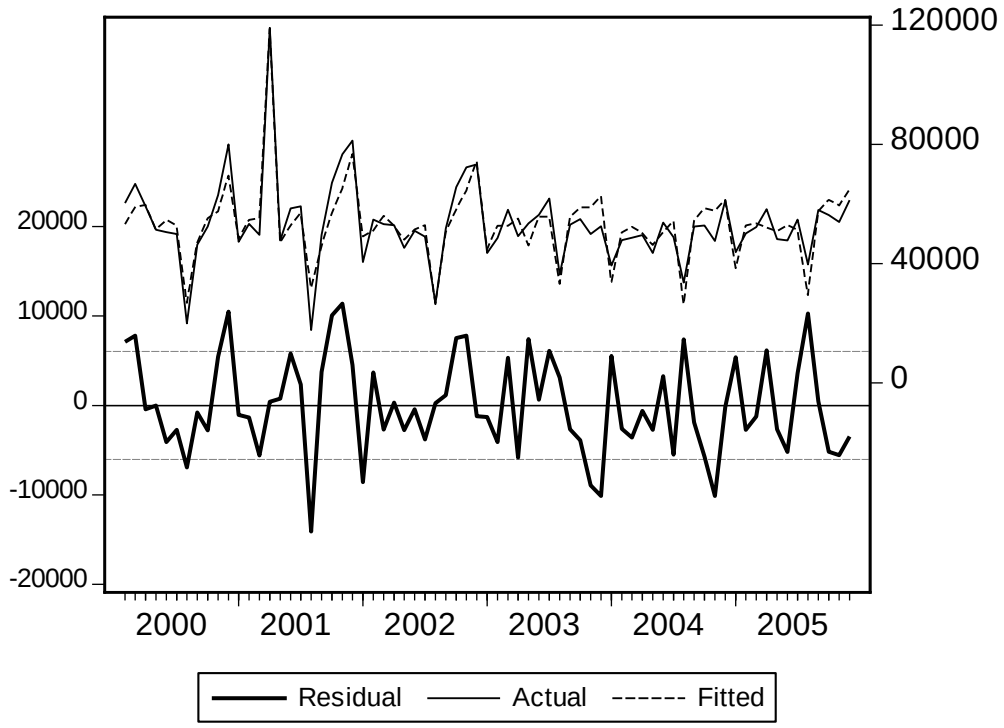
Dependent Variable: Y_t

Sample (adjusted): 2000M02 2005M12
Included observations: 71 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
Intercept	42197.82	3120.978	13.52070	0.0000
AR(1)	0.529408	0.114203	4.635687	0.0000

R-squared	0.842814	Mean dependent var	53315.55
Adjusted R-squared	0.806964	S.D. dependent var	13776.55
S.E. of regression	6052.843	Akaike info criterion	20.42918
Sum squared resid	2.09E+09	Schwarz criterion	20.87534
B_G LM Statistic:	1.743922;	Prob. F(6,51)	0.129785
Q Statistic	8.9531;	Prob. Chi-Square(6)	0.111

* Seasonal and shift dummies were included but their estimated coefficients of are not reported. AR(1) captures the residual dynamics.



1.18. Regression Analysis of the Data from Hospital Number 18

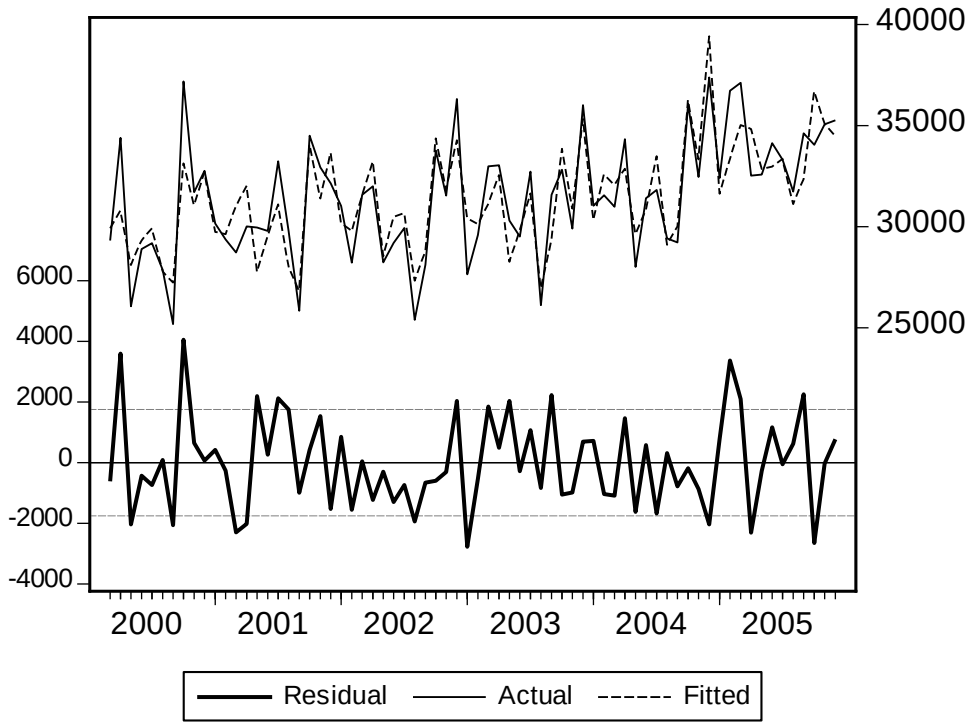
Dependent Variable: Y_t

Sample (adjusted): 2000M03 2005M12
Included observations: 70 after adjustments

Variable*	Coefficient	Std. Error	t-Statistic	Prob.
A_t	-15.15090	8.088878	-1.873053	0.0667
A_{t-1}	-4.288404	1.891701	-2.266957	0.0276
R_t	21.03824	9.909456	2.123047	0.0385
L_t	5660.750	1959.943	2.888222	0.0056
L_{t-1}	-3961.802	1887.002	-2.099522	0.0406
Intercept	5376.520	8059.662	0.667090	0.5077
t	47.11114	12.38936	3.802549	0.0004

R-squared	0.734381	Mean dependent var	31425.59
Adjusted R-squared	0.647544	S.D. dependent var	2959.521
S.E. of regression	1757.010	Akaike info criterion	17.99765
Sum squared resid	1.61E+08	Schwarz criterion	18.57583
B_G LM Statistic:	0.605585;	Prob. F(6,46)	0.724439
Q Statistic	5.7784;	Prob. Chi-Square(6)	0.448

* Seasonal dummies were included but their estimated coefficients of are not reported.



Appendix A.7.1: ESAC POINT PREVALENCE DATA COLLECTION FORM

ESAC Point Prevalence Survey May 2006

Date of survey	
Auditor code	
Hospital	
Department (or Group or Division)	
Denominator: total patients in Department (including patients in Intensive Care Units or High Dependency Units) at 08.00	

Note: The aim is to find out what the physicians think they are treating. For this we will look at all patient records, and may request additional information from nurses, pharmacists or doctors. There will be no discussion about the appropriateness of prescribing. The staff should not have the feeling that we are checking them and there is no intention to change prescribing.

Include in survey: all patients who are receiving systemic (not topical) antibacterials (not antifungals or antivirals or TB treatment). All patients who are in the hospital at 8 am on the days of survey should be included in the study.

Prophylaxis: any patient who received one or more doses in the 24h prior to 8am on the day of the survey. NB, check doses received on the previous day as well in order to code as either 1 dose, 24hours or >24hours.

Diagnosis Group: by anatomical site of infection treated or prevented (prophylaxis).

Site	Codes	Examples
CNS	Proph CNS	Prophylaxis for CNS (neurosurgery, meningococcal)
	CNS	Infections of the Central Nervous System
EYE	Proph EYE	Prophylaxis for eye operations
	EYE	Endophthalmitis
ENT	Proph ENT	Prophylaxis for Ear, Nose or Throat (surgery or medical)
	ENT	Infections of ear, mouth, nose, throat or larynx
RESP	Proph RES	Pulmonary surgery, prophylaxis for respiratory pathogens
	Bron	Acute bronchitis or exacerbations of chronic bronchitis
	Pneu	Pneumonia
CVS	Proph CVS	Cardiac or vascular surgery, endocarditis prophylaxis
	CVS	Cardiovascular infections: endocarditis, vascular graft
GI	Proph GI	Surgery of the GI tract, liver or biliary tree, GI prophylaxis in neutropenic patients or hepatic failure
	GI	GI infections (salmonellosis, antibiotic associated diarrhoea)
	IA	Intra-abdominal sepsis including hepatobiliary
SSTBJ	Proph SBJ	Prophylaxis for plastic or orthopaedic surgery (bone or joint)
	SST	Cellulitis, wound, deep soft tissue not involving bone
	BJ	Septic arthritis (including prosthetic joint), osteomyelitis
UTI	Proph UT	Prophylaxis for urological surgery, recurrent UTI
	Cys	Lower UTI
	Pye	Upper UTI
GUOB	Proph GyOb	Prophylaxis for obstetric or gynaecological surgery
	OBGY	Obstetric or gynaecological infections, STD in women
	GUM	Prostatitis, epididymo-orchitis, STD in men
Not Defined	BAC	Bacteraemia (not endocarditis) with no clear anatomical site
	SIRS	Systemic inflammatory response with no clear anatomic site
	UND	Completely un-defined site with no systemic inflammation

Hospital	Department	Full patient identifier[a]	Survey Number[b]	Sex	Ward (including ICU)

[a]For example 10 digit unique hospital number, to allow local linkage to patient records for more detailed audit. This identifier is not included in the ESAC on-line database
[b]A unique but non-identifiable number for each patient entered in the survey by this hospital. This number will be included in the ESAC on-line database to allow queries about data entered on the web-site. It is suggested that patients are numbered consecutively before entry onto the database.

Essential Fields						Essential Fields				
Drug	Unit Dose[1]	Doses per day[2]	Route[3]	Diagnosis (site)[4]	Indication[5]	Immuno-suppression[6]	Foreign material[7]	Culture pre-therapy[8]	Reason in notes[9]	Assessment[10]
1										
2										
3										
4										
5										

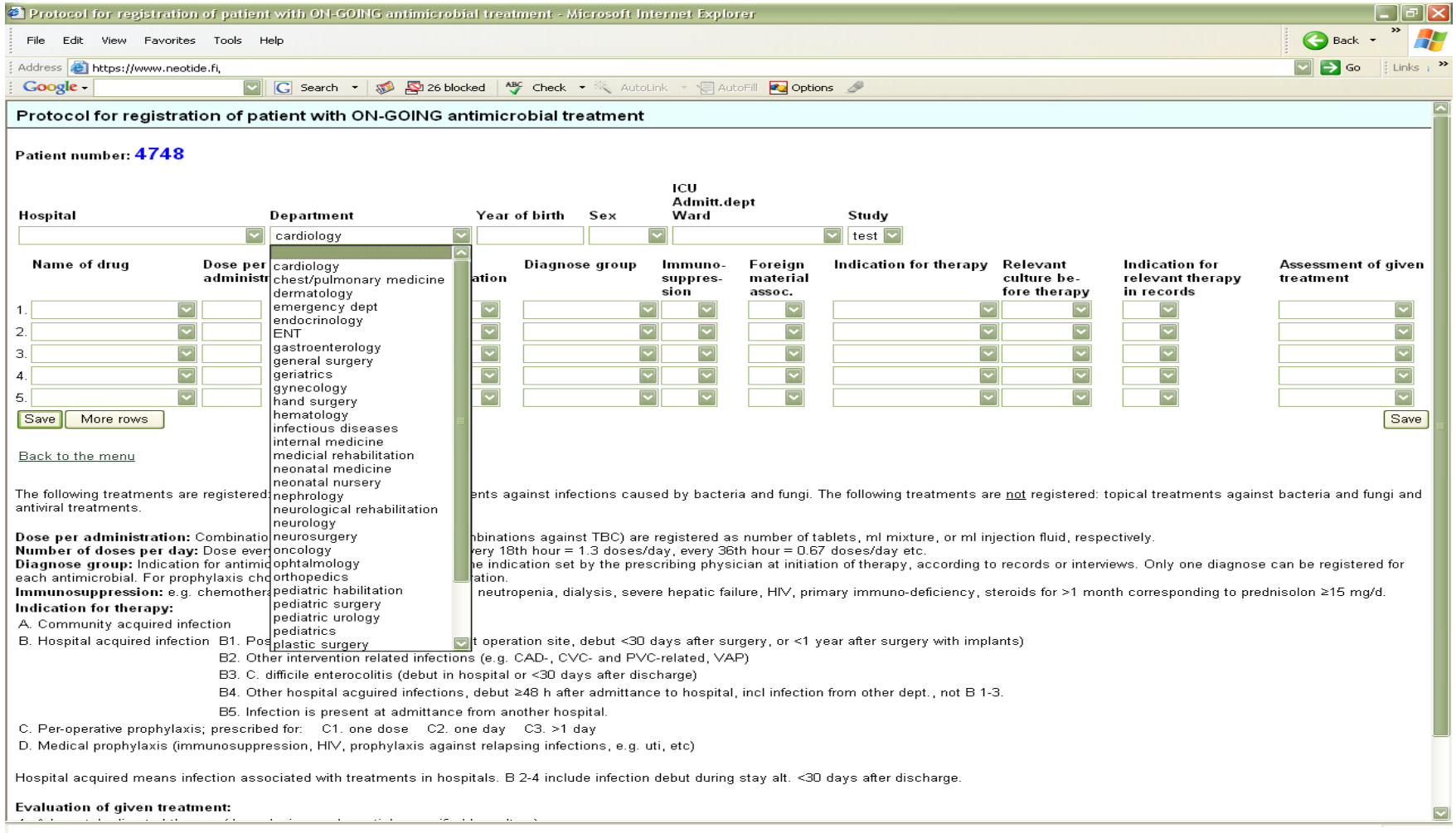
[1]Dose per administration in grams: for combination products record the total dose prescribed (e.g. co-amoxiclav 1.2 G; co-trimoxazole 0.96 G.
[2]Provide fractions of doses if necessary, e.g. every 16h = 1.5 doses per day, every 36h = 0.67 doses per day, every 48h = 0.5 doses per day
[3]IV, oral, rectal
[4]See list on Page 1
[5]Indication codes:

A Community acquired infection	Symptoms or antibiotics started <48h after patient was admitted		
B Hospital acquired infection Symptoms start 48h after admission to hospital	B1 Post-operative infection (within 30 days after surgery or 1 year after implant surgery)		
	B2 Other intervention related infections (IV catheter, VAP, CAPD)		
	B3 *C difficile* associated diarrhoea >48h after admission or <30 days after previous admission		
	B4 Other hospital acquired infection		
	B5 Infection present on admission from another hospital		
C Surgical prophylaxis	C1 Single dose	C2 one day	C3 >1 day
D Medical prophylaxis			

[6]As defined by CDC contra-indication to live vaccines: cancer, leukaemia, HIV infection, primary immunodeficiency, cytotoxic chemotherapy, radiotherapy or high dose steroids (equivalent to prednisolone 15mg per day or more for 1 month or more, Yes or No.
[7]Infection associated with implanted device (prosthetic joint, pacemaker, IV line), Yes or No
[8]Relevant culture taken before antibiotic treatment was started, Yes or No
[9]A diagnosis or indication for treatment was recorded in the notes at the start of antibiotic treatment
[10]Assessment of concordance with local antibiotic policy

1. Concordant, culture positive
2. Concordant, culture negative (includes prophylaxis that is concordant with antibiotic policy)
3. Excessive but likely to be effective (e.g. meropenem for community acquired cellulitis)
4. Possibly ineffective (e.g. omission of treatment for anaerobic bacteria with intra-abdominal sepsis)Other faults, specify

Appendix A.7.2: The STRAMA Web-based Patient Registry

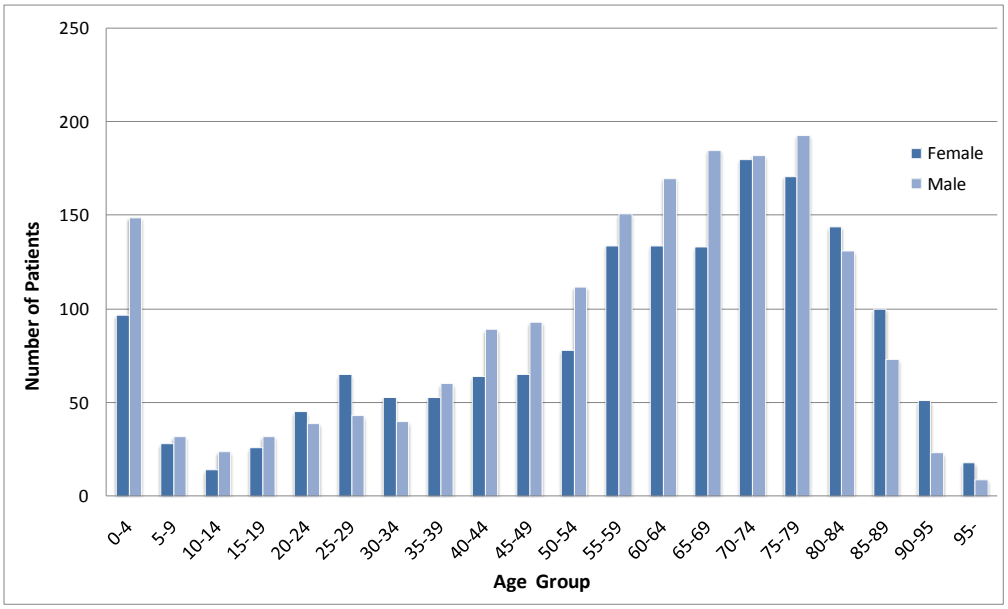


Appendix: A.7.3: Further analysis of ESAC Point Prevalence Survey

7.3.1 Prevalence of antibacterial treatment by patients

Of the total 3,483 treated patients, 1,653 (47.5%) were female, with 226 (6.5%) aged 5-16 years, and 145 (4.2%) aged <5 years (Figure A.7.3.1). Mean ages of treated patients were: 55.9 (SD 25 years), 57.4 (SD 24.9 years) in females and 54.6 (SD 25 years) in male patients. On average, each of the treated patients received 1.36 antibacterials. Female and male patients received 1.32 (2,182/1,653), and 1.40 (2,566/1,830) antibacterials, respectively. In twenty age groups the number of antibacterials per patient did not significantly different between men and women (P=0.55). Exposure to multiple antibacterial therapies was more likely in younger and older patients. The number of antibacterial therapies per patient for specific age groups was: 1.40 for age < 5 years old, 1.33 for age<17, 1.36 for age≥65, and 0.73 for all other ages.

Figure A.7.3.1: Distribution of Patients Received Antibacterials by Age Group and Sex



7.3.2 Prevalence of documentation of indication in case notes in hospitals

Indication Not Documented (IND) in case notes for all oral antibacterials ranged from 0% in hospital number 22 to 52% in hospital number 6 (mean 13.8%, SD 15.2). Prevalence of IND for all parenteral therapies was as low as 0.9% in hospital number 1 up to 100% in hospital number 22 (mean 27.4%, SD 27.5%). For all administration routes, prevalence of IND varied from 2% in hospital number 7 to 100% in hospital number 16 and 22 (mean 36.3%, SD 34.1). Only in three (15%) of the hospitals (numbers 2, 7, and 22) was IND for all drugs and all administration routes less than 10%, while in nine (45%) hospitals (numbers 4, 5, 6, 9, 11, 16, 17, 19 and 20) prevalence of IND was more than 25% for all drugs and all administration routes. (Table A.7.3.1)

Table A.7.3.1: Indication Not Documented (IND) in case notes in each of the hospitals

	IND by route for all drugs (%)		IND for all drugs (%)
Hospital number	Oral	Parenteral	Total
1	10.2	0.9	11.1
2	0.6	2.9	3.5
3	16.0	2.0	18.0
4	9.8	39.3	49.1
5	7.8	17.8	25.6
6	52.5	37.6	90.1
7	1.0	1.0	2.0
8	5.6	2.0	7.6
9	7.0	43.7	50.7
10	8.9	12.2	21.0
11	46.2	52.3	98.6
14	10.2	6.3	16.5
15	3.6	21.1	24.7
16	29.6	70.4	100.0
17	7.4	46.2	53.5
18	3.6	8.9	12.6
19	9.4	18.0	27.3
20	38.0	57.3	95.3
21	9.5	7.6	17.1
22	0.0	100.0	100
Mean (SD)	13.8 (15.2)	27.4 (27.5)	36.3 (34.1)
Total	13.4	22.3	35.7

7.3.3 Prevalence of taking relevant cultures before antibacterial therapy

Adult patients received 1,544 oral antibacterials. Relevant cultures had not been taken before starting oral therapy in 55% of patients. For 2,696 parenteral therapies in adult patients, relevant cultures had not been taken before starting therapy in 53% of patients. For children, relevant cultures had not been taken in 45% (unknown in 1%). Children received 142 oral antibacterials, with cultures not taken in 56%, compared to 40% of 364 parenteral antibiotics (Table A.7.3.2). Children were somewhat more likely to have cultures taken before commencing therapy, and case note documentation was more complete than in adults.

Table A.7.3.2: Prevalence of taking cultures before starting antibacterial therapy in adult and children given as percentage for total antibacterial therapies for two patient groups.

Adults (aged17 & over)	Yes	No	Unknown
Oral	40.6%	55.1%	4.3%
Parenteral	44.3%	53.0%	2.7%
Children (aged <17)			
Oral	42.3%	55.6%	2.1%
Parenteral	59.1%	40.1%	0.8%

Table A.7.3.3 shows the prevalence of taking cultures before antibacterial therapy for Community Acquired Infection (CAI) and Hospital Acquired Infection (HAI) by the number of antibacterial therapies. Taking relevant microbiological tests was more common in HAI (58.1%) than in CAI (52.8%).

Table A.7.3.3: Prevalence of taking cultures before treatment by percentage for total number of antibacterial therapies for CAI (community acquired infection) and HAI (hospital acquired infection)

	CAI	**HAI**
Yes (%)	52.8	58.1
No (%)	44.1	37.8
Unknown (%)	3.1	4.1

7.3.4 Analysis by clinical groups

On the day of the survey, distribution of the total of 3,483 treated patients in 6 main departments including Departments of Medicine, Surgery, ICU, Paediatrics, Obstetrics & Gynaecology, and Geriatric medicines was 41.1% (1,432), 35.5% (1,237), 7.2% (250), 10.7% (371), 4.7%(182) and 0.32% (11), respectively. The proportion of all antibacterial therapies (4,748) in the departments of Medicine, Surgery, ICU, Paediatrics, Obstetrics & Gynaecology, and Geriatric Medicine was 41% (1,964), 34.6% (1,657), 8.1% (386), 10.6% (506), 4.7% (224) and 0.2%, respectively. The total use of antibacterials was 5,916 DDD. In Table A.7.3.4, more measures are provided for each clinical group. The percentage of prescribed daily doses (PDD) has the same ranking as the use in DDD. The ratio of PDD to DDD in different departments is more than 1.8 (other departments including Geriatric Medicine and Genecology & Obstetrics) suggesting that the total use in DDD for hospitals overestimates the number of patients

exposed to antibacterial therapy. The noteworthy finding is the higher ratio PDD/DDD in Paediatrics (2.1) than in Medical Departments (1.9) (Table A.7.3.4).

Table A.7.3.4: Prevalence of antibacterials prescribed in main clinical groups. Other includes Geriatrics Medicine and Genecology & Obstetrics. PDD: Prescribed Daily Dose, AB: Antibacterial

Clinical group	Medicine	Surgery	ICU	Paediatrics	Other
Number of patients	1432	1237	250	371	193
% of total	41.1	35.5	7.2	10.7	5.5
Number of therapies	1964	1657	386	506	235
% of total	41.0	34.6	8.1	10.6	4.9
Number of DDDs	2689	2083	537	371	236
% of total	45.5	35.2	9.1	6.3	4.0
Number of PDDs	5,201	4,480	1,371	773	420
% of total	42.5	36.6	11.2	6.3	3.4
PDD/DDD	1.9	2.2	2.6	2.1	1.8
DDD/AB	1.4	1.3	1.4	0.7	1.0
DDD/Patient	1.9	1.7	2.1	1.0	1.2
PDD/ Patient	3.6	3.6	5.5	2.1	2.2
Number of AB/patients	1.4	1.3	1.5	1.4	1.2

7.3.5 Analysis by anatomic site of therapy

The greatest proportion of antibiotics were used in treating infections in the respiratory tract (24.1%), followed by Skin, Soft Tissue, Bone & Joint (SSTBJ) (18.1%), undefined site (15.8%), intra-abdominal (15%) and urinary tract (13.3%). The undefined site included bacteraemia, Systemic Inflammatory Response Syndrome (SIRS) with no clear anatomic site, and undefined site with no systemic inflammation. The prevalence of patients who received antibacterials for five other anatomic sites was less than 5%. The commonest anatomical systems were the respiratory tract (28.9%) for treatment and intra-abdominal (22.9%) for prophylaxis (Table A.7.3.5). The anatomical system was undefined for 569 (15.8%) patients: 275 of these patients had sepsis, 168 of these had

bacteraemia with no defined site of origin. One hundred and twenty-six antibacterials were prescribed to patients with an undefined site of infection and with no systemic inflammation. The proportion of patients who received antibacterials for prophylaxis after intra-abdominal surgery were higher for SSTBJ, Otorhinolaryngology, and undefined with 15.6%, 13.5% and 12.3% respectively for these anatomic sites. In the treatment group following the respiratory tract, the other main anatomic sites more prevalent among treated patients were SSTBJ (18.8%), Undefined (16.9%) and urinary tract (13.5%) were the other anatomic sites more prevalent among treated patients.

Table A.7.3.5 Anatomical sites recorded for treatment and prophylaxis. The total (3,599) is greater than the number of patients treated (3, 483) because some patients had antibacterials prescribed for more than one anatomic site.

System	Diagnosis site	%	Prophylaxis	% total prophylaxis	Treatment	% total treatment
Respiratory	867	24.1%	69	8.2%	798	28.9%
Skin, Bone & Joint	650	18.1%	131	15.6%	519	18.8%
Undefined	569	15.8%	103	12.3%	466	16.9%
Intra-abdominal	540	15.0%	192	22.9%	348	12.6%
Urinary tract	471	13.1%	99	11.8%	372	13.5%
Otorhinolaryngology	163	4.5%	113	13.5%	50	1.8%
Genital	133	3.7%	78	9.3%	55	2.0%
Cardiovascular	108	3.0%	29	3.5%	79	2.9%
CNS	86	2.4%	21	2.5%	65	2.4%
Eye	12	0.3%	4	0.5%	8	0.3%
Total	3599		839		2760	

7.3.6 Analysis by indication

In total, 3,587, indications were recorded for 3,483 patients, of which 104 applied to patients with more than one indication. CAI was the indication in 47.5% (1703/3,587), compared to HAI 28.9% (n=1038), surgical prophylaxis for 16.8% (n=602), and medical prophylaxis for 6.8%. More patients therefore received antibacterials for treatment (76.4%) than for prophylaxis (23.6%) (Table A.7.3.6).

Table A.7. 3,6: Indication for therapy

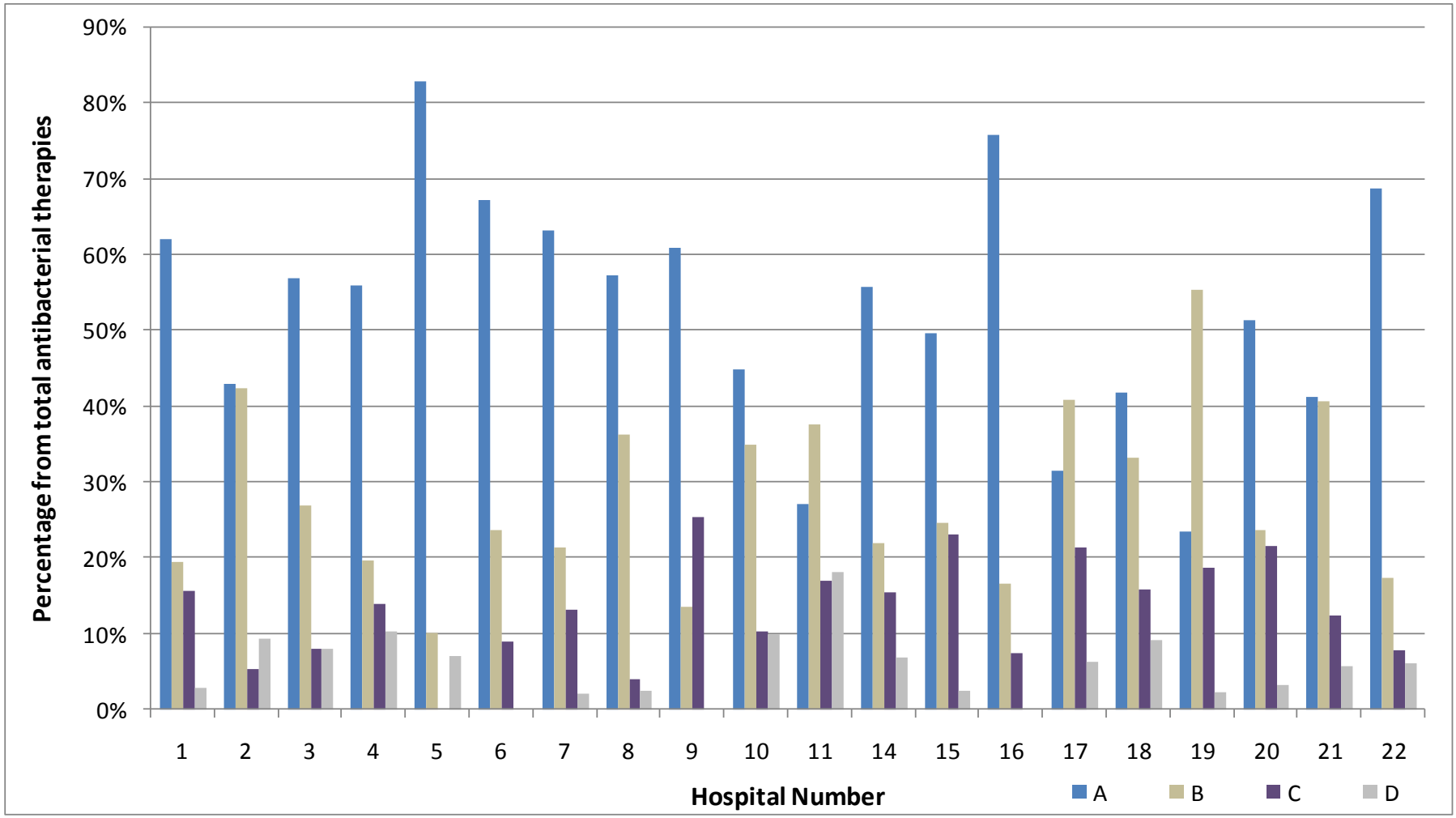
Indication for therapy	Number of patients	Percentage of total patients
A. Community acquired infection	***1,703***	***47.5%***
B1. Postoperative infection	307	8.6%
B2. Other intervention related infections	145	4.0%
B3. C. difficile enterocolitis	33	0.9%
B4. Other hospital acquired infections	492	13.7%
B5. Infection is present at admission from another hospital	61	1.7%
B. Hospital acquired infection total	***1,038***	***28.9%***
C1. prophylaxis one dose	155	4.3%
C2. prophylaxis one day	99	2.8%
C3. prophylaxis >1 day	348	9.7%
C. Surgical prophylaxis total	***602***	***16.8%***
D. Medical prophylaxis	***244***	***6.8%***
Grand Total	**3,587**	

Analysis by indication in each of the hospitals

Analysis of indication by hospital shows that in 16 out of 20 (80%) of hospitals, CAI was the commonest indication. In three hospitals (numbers 11, 17, and 19) hospital acquired infections was the commonest indication for treatment and in one hospital (number 21) a roughly equal number of patients were treated for CAI or HAI. The percentage of antibacterial therapies for CAI ranged from 23.5% in hospital number 19

to 83% in hospital number 5 (mean 53.1%, SD 16%). The prevalence of HAI varied from 28% in hospital number 5 to 42.3% in hospital number 2 (mean 28%, SD11.6%). For surgical prophylaxis, the percentage of prescribed antibacterials varied from 0% in hospital number 5 to 25.3% in hospital number 9 (mean 13.3%, SD 6.8%). The proportion of antibacterials used for medical prophylaxis ranged from 0% in hospital number 9 to 18.2% in hospital number 11 (mean 5.6%, SD 4.5%) (Figure A.7.3.2). Regarding the mean and standard deviations, the variations between the hospitals by antibacterial therapy was highest for CAI followed by HAI, surgical prophylaxis, and medical prophylaxis. For this and other analyses by hospital, it is noteworthy to remember that hospitals 5 and 17 were infectious diseases hospitals.

Figure A.7.3.2: Indication for antibacterial therapy presented as percentage from total therapies in each hospital. A: Community acquired infection, B: Hospital acquired infection, C: Surgical prophylaxis, D: Medical prophylaxis

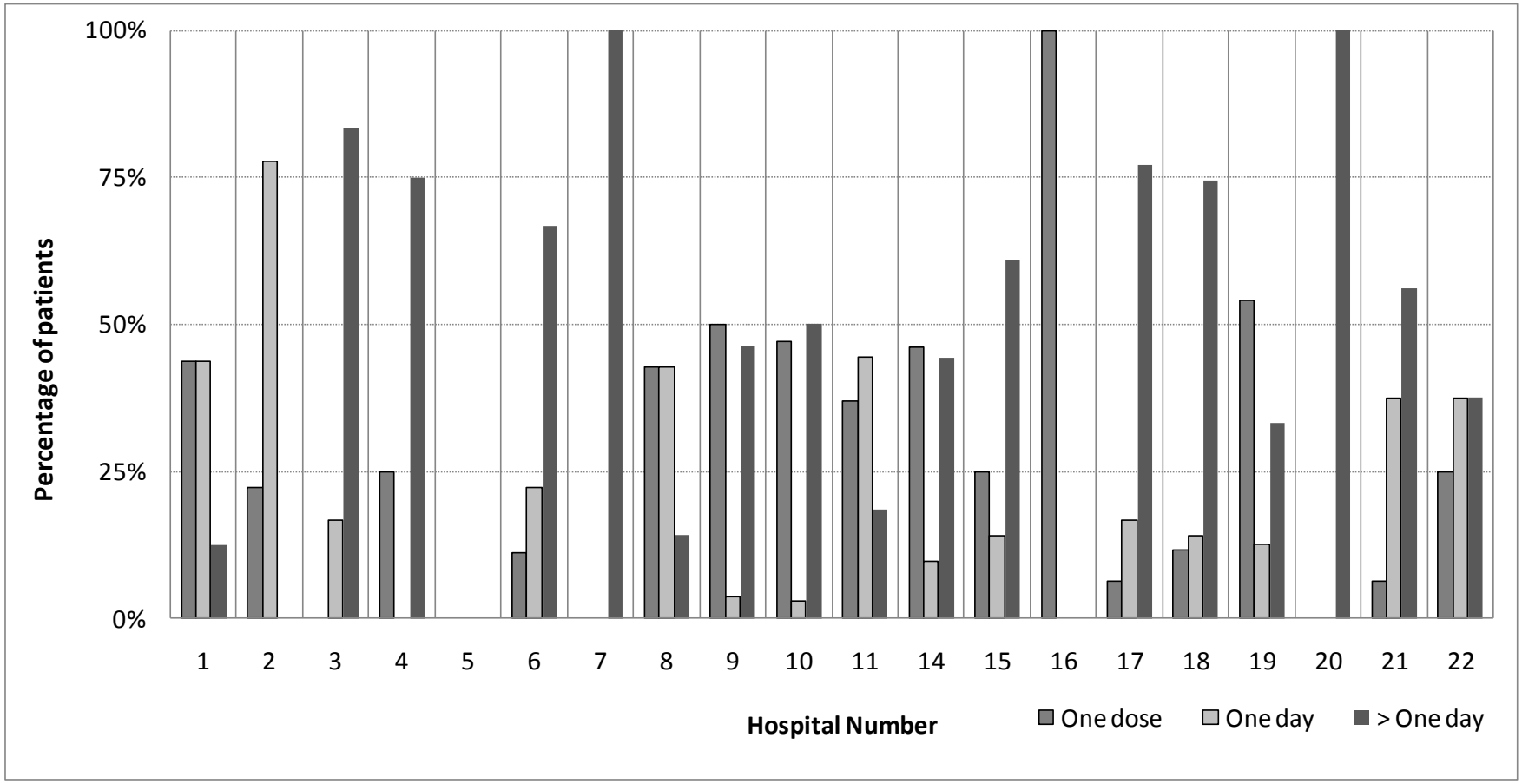


7.3.7 Antibacterial use for surgical prophylaxis

Duration of surgical prophylaxis antibacterial therapy in each of the hospitals

The number of patients in each hospital who received antibacterials for surgical prophylaxis ranged from 2 in hospital number 16 to 86 in hospital number 18 (mean 31.2, median 24, SD 24.6). The proportion of patients given surgical prophylaxis who received one dose ranged from 0% in hospitals number 3, 7, and 20, to 54% in hospital number 19 (mean 29.1%, SD 25.6%). One-day prophylaxis ranged from 0% in hospitals 4, 16, and 20, to 44.5% in hospital number 22 (mean 20.6%, SD 20.1%). Prevalence of receiving more than one day pre-operative prophylaxis ranged from 0% in hospitals 2 and 16, to 100% in hospital number 20 (mean 50.3%, SD 30.9%) (Figure A.7.3.3). The mean number of patients was higher in more than one-day duration and the convergence of hospitals was less in number of patients of more than one-day surgical prophylaxis than 2 other durations (comparing standard deviations of mean for three durations). The number of antibacterials for each of the patients receiving pre-operative prophylaxis varied from 1 antibacterial to 2 for all three durations of treatment but was different across the hospitals.

Figure A.7.3.3: Duration of surgical prophylaxis presented as percentage from total number patients received antibacterials for this indication in each hospital.



Most commonly prescribed antibacterials for surgical prophylaxis

Prescribed doses for the most commonly prescribed antibacterials for each of the differing surgical prophylaxis durations are shown in table A.7.3.7, although these only account for a relatively small proportion of all antibiotics used. The ratio of PDD/DDD for the three most commonly prescribed antibacterials is less than 0.5, while it is close to one for one-day prophylaxis and close to more than 1 for four top antibacterials used for >one-day duration. Antibacterials for one dose and one-day prophylaxis are most commonly parenteral while for > one-day, one of them is oral (Amoxicillin and enzyme inhibitor (EI) or Co-amoxiclav). Two common antibacterials in three categories are Cefazoline and Parenteral Cefuroxime. For Cefazoline the PDD/DDD increases with duration of prophylaxis for 0.4 to 1.3. For Cefuroxime the ratio is lower in one dose than 2 other durations. It suggests that in surgical prophylaxis the prescribed dose can increase with the duration of prophylaxis and lead to more antibacterial consumption. This was investigated for some other antibacterials and the finding was the same (data not shown).

Table A.7.3.7: Most commonly prescribed antibiotics in each group of surgical prophylaxis and the ratio of Prescribed Daily Dose (PDD) to DDD.

		One dose	**One day**	**> One day**
1	*AB*	Cefazoline P	Cefazoline P	Cefuroxime P
	Percentage	35.9%	31.3%	17.2%
	PDD/DDD	0.4	1.0	0.8
2	*AB*	Cefuroxime P	Cefuroxime P	Amoxicillin & EI, O
	Percentage	17.6%	25.0%	12.7%
	PDD/DDD	0.5	0.9	1.7
3	*AB*	Amoxicillin & EI, P		Metronidazole P
	Percentage	11.8%		12.7%
	PDD/DDD	0.4		1.0
4	*AB*			Cefazoline P
	Percentage			10.8%
	PDD/DDD			1.3
Number of therapies		170	112	425

7.3.8 Antibacterial use for community acquired infection (CAI)

Analysis of CAI by 1,729 anatomical sites of infection found 1,703 patients who were treated for infections and received 2,299 antibacterials in 3,157 DDD, equivalent to 1.33 antibacterials per patient and 1.83 DDDs per patient on the day of survey. There were substantial variations in the number of prescribed antibacterials with the number of DDDs by anatomic sites of infection. Therefore, data were examined for the three most commonly prescribed antibacterials (providing that each was used at least 10 times) by anatomic site of infection and their relevant ratios of PDD to DDD (Table A.7.3.8). The top three antibacterials varied with site of infection. Of the 16 antibacterials listed in the table, the ratio of PDD/DDD was <1 in 3, equal to 1 in 5, and >1 in 7 antibacterials. Cefuroxime was among the top antibacterials for 4 sites of infection, but with different ratios of PDD/DDD for different sites of infection: intra-abdominal (1.1), respiratory

(0.9), undefined (1.2), and urinary tract (1.2). Alert Antibacterials feature in four of the 16 cells: Gentamicin (2 times), Ceftriaxone, and parenteral Ciprofloxacin. Oral Amoxicillin & EI used in respiratory and urinary tract infections had different PDD/DDD ratios of 1.7 and 1.8. There were large differences in Gentamicin dosing for cardiovascular versus undefined infections with the ratios being 1.6 versus 0.7. Benzylpenicillin used in SSTBJ with a PDD/DDD ratio of 2.2 was the highest in the table. Average prescribed doses to the DDDs was higher in SSTBJ followed by respiratory, urinary tract, intra-abdominal and undefined infections.

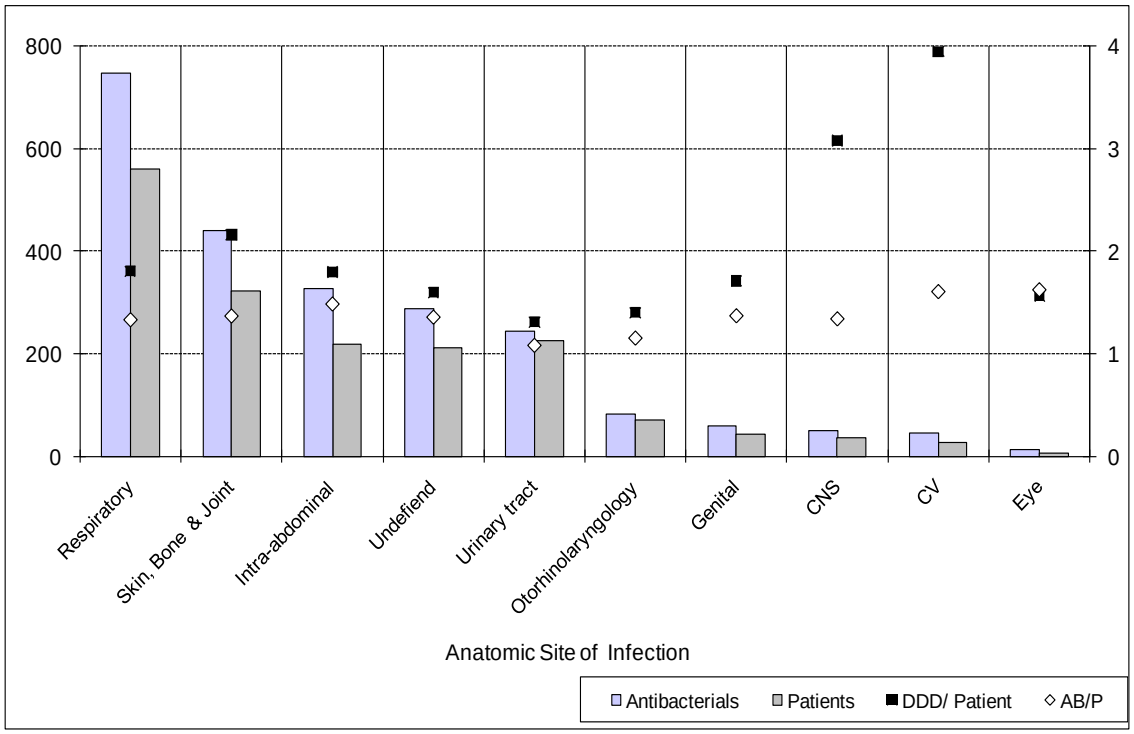
Table A.7.3.8 Three most commonly antibacterials prescribed at least 10 times for treatment of community acquired infection by anatomic site of infection, and the relevant ratio of PDD to DDD

Diagnosis site	1st AB, PDD/DDD		2nd AB , PDD/DDD		3rd AB, PDD/DDD	
Cardiovascular	Gentamicin P	1.6				
Intra-abdominal	Metronidazole P	1	Ciprofloxacin O	1	Cefuroxime P	1.1
Respiratory	Amoxicillin & EI, P	1	Amoxicillin & EI, O	1.7	Cefuroxime P	0.9
SSTBJ	Ciprofloxacin O	1	Clindamycin P	1.1	Benzylpenicillin P	2.2
Undefined	Ceftriaxone P	0.9	Cefuroxime P	1.2	Gentamicin P	0.7
Urinary tract	Ciprofloxacin P	0.9	Amoxicillin & EI, O	1.8	Cefuroxime P	1.2

Antibacterial use for Community Acquired Infection by anatomic site of infection

Figure A.7.3.5 shows antibacterial use by anatomic sites of infection for CAI. Patients were most commonly treated for CAI infections of the respiratory tract (32.4%), SSTBJ (19.1%), and intra-abdominal (14.2%) followed by undefined site (12.5%) and urinary tract (11%). The number of antibacterials per patient ranged from 1.1 in urinary tract infections to 1.63 in eye infection (mean 1.37, SD 0.17 antibacterial per patient). Mean DDDs per patient varied from 1.31 for urinary tract to 3.95 for cardiovascular infections (mean: 2.04, SD 0.84 DDDs per patient). There is large variation in the number of DDDs per patient by anatomic site of infections with no significant association between DDD/Patient and AB/Patient for different anatomic sites of infection (correlation coefficient 0.49, P=0.15).

Figure A.7.3.5: Antibacterial use by site of infection for Community Acquired Infection.



Antibacterial use for Community Acquired Infection in hospitals

Table A.7.3.9 shows details of antibacterial use for CAI by hospital. The proportion of treated patients receiving antibacterials for CAI ranged from 24% in hospital 19 to 85% in hospital number 5 (mean 52.2%, SD 15.7%). In 10 hospitals the prevalence was more than 50% and in 2 hospitals it was less than 30%. For all antibacterial use, the mean percentage of antibacterials used for CAI was 53% (SD 16%) and it ranged from 23.4% in hospital number 19 to 83% in hospital number 5. The percentage of DDD for CAI varied from 31% in hospital number 19 to 88% in hospital number 5 (mean 57.5%, SD 14.4%). The number of antibacterials per patient was higher than 1 in all hospitals, varying from 1.01 in hospital number 6 to 1.63 in hospital number 14 (mean 1.32, SD 0.16). The number of DDD/Patient ranged from 1.11 in hospital number 22 to 2.80 in hospital number 4 (mean 1.84, SD 0.44). The ratio of PDD/DDD for CAI ranged from 1.32 in hospital number 8 to 2.37 in hospital number 2 (mean 1.89, SD 0.32). Ranking the hospitals by each of the 5 measures presented in Table A.7.3.9. and comparing them with each other gives 5 different sorted tables with some similarities. Hospitals have similar rankings for the first 3 measures (% patients, % antibacterial therapies and %DDD, all from the total). One hospital has the same position for 3 measures above the mean and 6 hospitals have the same positions below the mean. With regards to two other measures, AB/patient and PDD/DDD, apart from one hospital, all other hospitals had different positions either in their position from the mean or in general. It suggests that in most of the hospitals, CAI, none of the measures by themselves can fully describe antibacterial use. The first three measures are mostly about casemix and the second set of two measures are about antibiotic choice. With regards to means and standard deviations there is large variation across hospitals for all measures, especially for prevalence of CAI from total patients, percentage of antibacterials from the total, and percentage of use in DDD from the total use. Analysis of the data for prescribed

daily doses by anatomic site for each hospital could explain the variations between hospitals but this was beyond this chapter.

Table A.7.3.9: Antibacterial use by hospital for Community acquired Infection (CAI)

Hospital	% treated patients with CAI	% all AB therapies used for CAI	% of total DDDs used for CAI	AB/patient treated for CAI	PDD/DDD for patients treated for CAI
1	58.1	62	64.9	1.24	2.17
2	43.4	42.9	48.1	1.38	2.37
3	61.4	57	52.6	1.33	1.94
4	54	56.1	59.3	1.29	2.02
5	84.5	82.9	88.2	1.15	1.80
6	68.4	67.3	75.8	1.01	1.69
7	63	63.3	61.6	1.35	1.94
8	54.8	57.4	62.7	1.48	1.32
9	58.3	61	72.2	1.19	2.14
10	41.9	44.8	47.3	1.62	1.90
11	28.8	27.2	37.4	1.22	1.59
14	48.9	55.8	64.6	1.63	1.59
15	48.4	49.7	52.4	1.38	1.40
16	76.2	75.9	74.7	1.28	2.29
17	31	31.4	41.3	1.49	2.14
18	41.5	41.8	47	1.28	2.06
19	24.1	23.4	30.7	1.11	1.53
20	49.4	51.5	53.9	1.48	1.77
21	40	41.3	46.1	1.38	1.84
22	67.3	68.7	68.2	1.20	2.43
Mean	52.2	53.1	57.5	1.32	1.89
SD	15.7	15.6	14.4	0.16	0.32

7.3.9 Antibacterial use for hospital acquired infection (HAI)

The total number of patients treated for HAI was 1,015. Types of infections that were categorised under Hospital Acquired Infections were: post operative infection (n=307 patients), intervention related infection (n=145), C. Difficile enterocolitis (n=33), other hospital acquired infections (n=492), and infections present on admission from another hospital (n=61). For a small number of patients, there was more than one source of the HAI, with the 1,015 patients having 1,038 sources of HAI. The total number of antibacterials prescribed for HAI was 1,425. Four hundred and ten patients received more than one antibacterial for an HAI, of which 53 received 3 to 5 antibacterials. To allow more in-depth analysis by type of antibacterials used in each of the anatomic sites of infection, data were analysed for the top three antibacterials (providing that they were prescribed at least 10 times) and their ratio of PDD/DDD (Table A.7.3.9). Seven out of sixteen of the most commonly prescribed antibacterials by anatomic site of infection were Alert Antibiotics including: parenteral Vancomycin (3 times), Piperacillin & EI (2 times), Meropenem, and parenteral Ciprofloxacin. Most of the other antibacterials were broad-spectrum. Seven out of sixteen were oral antibacterials. Parenteral Vancomycin was the most commonly used antibacterial for CNS, SSTBJ, and undefined infections with a PDD/DDD ratio of less than 1 (from 0.7 to 0.8). Oral Ciprofloxacin, with 4 times the frequency in the table of top three antibacterials, had a PDD/DDD of 0.9 to 1.1. The average PDD/DDD of three top antibacterials was higher in SSTBJ, followed by respiratory, undefined, intra-abdominal and urinary tract infections. Overall, six out of the antibacterials in the table of top three had a PDD/DD ratio more than 1 (range 1.2 to 1.9); for seven the ratio was less than 1 (0.6 to 0.9) and in three remaining antibacterials it was equal to 1 (Table A.7.3.10).

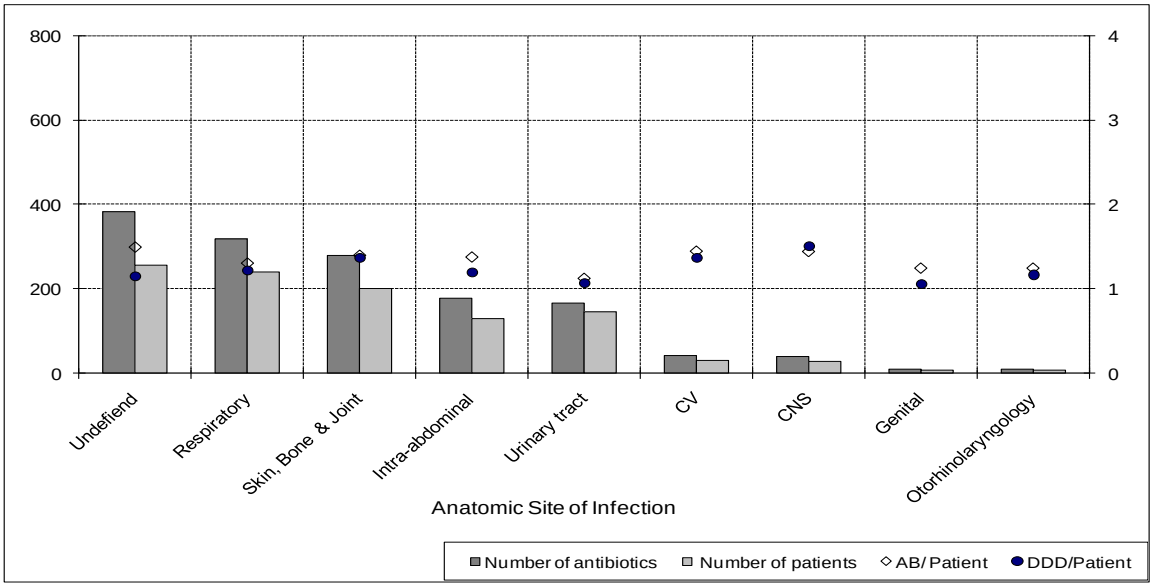
Table A.7.3.10: Three most commonly antibacterials prescribed at least 10 times for treatment of hospital acquired infection by anatomic site of infection, and the relevant ratio of PDD to DDD

Diagnosis site	1st AB, PDD/DDD		2nd AB, PDD/DDD		3rd AB, PDD/DDD	
CNS	Vancomycin P	0.7				
Intra-abdominal	Metronidazole O	0.6	Metronidazole P	1	Ciprofloxacin P	1.3
Respiratory	Piperacillin & EI, P	1	Ciprofloxacin O	1.2	Amoxicillin &EI, P	1.2
SSTBJ	Vancomycin P	0.8	Ciprofloxacin O	1.2	Amoxicillin &EI, O	1.9
Undefined	Vancomycin P	0.7	Piperacillin & EI, P	1	Meropenem P	1.6
Urinary tract	Ciprofloxacin O	0.9	Cotrimoxazole O	0.8	Norfloxacin O	0.9

Antibacterial use for Hospital Acquired Infection by anatomic site of infection

Analysis of HAIs infection by anatomic site of infection showed that 1,038 sources of HAI were associated with 1,043 anatomic sites of infection, with patients receiving 1,425 antibacterials in 1,738 DDD. The mean number of DDDs per patient was 1.2 and antibacterials per patient was 1.3. The commonest sites of infections were: undefined site of infection (24.5% of total HAIs) followed by respiratory infection (23%), SSTBJ (19(2%), urinary tract (14%), and intra-abdominal (12.3%). The percentage of total antibacterial therapies used for each site was undefined sites of infection (26.9% from total) followed by respiratory (23.3%), SSTBJ (19.7%) intra-abdominal (12.5%), and urinary tract infection (11.6%). The number of antibacterials per patients ranged from 1.1 for urinary tract infections to 1.5 for undefined infections (mean 1.35, SD 0.12). The number of DDDs per patient ranged from 1.1 in genital infection to 1.5 in CNS infection (mean 1.23, SD 0.15) (Figure A.7.3.6).

Figure A.7.3.6: Antibacterial use for hospital acquired infection (HAI) for different diagnosis sites measured by number of antibacterials number of patients, number of antibacterials per patient and number DDD per patient.



Antibacterial use for HAI by hospital

Antibacterial use for HAI by hospital is shown in Table A.7.3.11. The percentage of treated patients with an HAI ranged from 9.1% in hospital number 5 to 51.8% in hospital number 19 (mean 27.2%, SD 10.8%). The percentage of antibacterials used to treat HAIs ranged from 10.1% in hospital number 5 to 55.5% in hospital number 19 (mean 28%, SD 11.6%). The percentage of all antibacterial DDDs used to treat HAIs varied from 10.3% in hospital number 5 to 56% in hospital number 19 (mean 26.9%, SD 11.9%). The number of antibacterials prescribed for the treatment of HAIs per patient was higher than 1 in all hospitals, and varied from 1.09 in hospital number 6 to 1.67 in hospital number 17 (mean 1.4, SD 0.2). The average ratio of PDD to DDD for antibacterials in HAI indications was considerably more than one in all hospitals. The minimum was 1.62 in hospital number 15 and the maximum was as high as 4.55 in hospital number 9 (mean 2.3, SD 0.8). The ranking of the hospitals by the first 3 measures (% patients, % AB therapies, % of DDD of the total), and the other 2 measures (AB/patients and PDD/DDD) for both CAI (Table 7.13) and HAI (Table A.7.3.11) allowed a comparison between these two types of Acquired Infection. The hospitals above and below the mean are similar however, for 2 hospitals the positions above the mean are similar and for another 2 hospitals with positions below the mean the ranks are the same for the first 3 measures. For the other 2 measures, the ranking positions are quite similar for all hospitals. The standard deviations of AB/Patient and DDD/Patients are relatively low, indicating less variability of these two measures based on anatomic sites of infection. There is a significant and positive association between DDD/patients and AB/patients (correlation coefficient= 0.65, P=0.05).

Standard deviations from mean for each of the 5 measurements show large variations across the hospitals for nearly all measures, however, the number of antibacterials per patient had less variation than the others. Nonetheless, the variations are less than the same measures for CAI.

Table A.7.3.11: Antibacterial use for hospital acquired infection (HAI) by means of number of treated patients, Antibacterial (AB) therapies, DDD from total in the survey, number of antibacterials per patient and PDD to DDD ratios.

Hospital	% Patients	% AB therapies	% DDD	AB/patient	PDD/DDD
1	21.5	19.4	18.6	1.05	1.79
2	38.5	42.4	39.4	1.53	3.23
3	24.3	27.0	23.6	1.59	1.84
4	18.0	19.7	17.4	1.36	2.38
5	9.1	10.1	10.3	1.44	1.52
6	22.4	23.8	18.2	1.09	2.13
7	20.5	21.4	20.7	1.40	1.65
8	37.9	36.3	34.5	1.42	1.77
9	12.8	13.6	11.3	1.21	4.55
10	34.6	34.9	34.3	1.59	2.15
11	36.3	37.6	36.3	1.34	2.69
14	23.1	22.0	22.0	1.38	2.09
15	23.4	24.7	25.7	1.41	1.62
16	19.0	16.7	14.3	1.13	2.58
17	36.5	40.8	39.0	1.67	4.06
18	32.6	33.2	32.0	1.34	2.40
19	51.8	55.5	56.0	1.25	2.31
20	23.6	23.7	23.8	1.48	1.63
21	40.4	40.6	42.1	1.44	2.39
22	17.3	17.4	17.6	1.18	1.98
Mean	27.2	28.0	26.9	1.4	2.3
SD	10.8	11.6	11.9	0.2	0.8

7.3.10 Combination therapy

To assess the number of prescribed antibacterials for each patient, data were analysed for patients receiving one, two, three, and >3 antibacterials (Table A.7.3.12). The total (3,599) is greater than the number of patients treated (3, 483) because some patients had antibacterial prescribed for more than one anatomic site**.** In total 65.3% (n=2,381) of patients received only one antibacterial while 30.2% (n=1,102) of them were treated with two drugs. Up to three antibacterials were prescribed for 4% (n= 147) and four or five antibacterials for 0.4% (n=16) of patients. Mono-therapy ranged from 97% (hospital number 6) to 47% (hospital number 10) with a median of 67% and SD of 13%. Incidence of receiving up to two antibacterials ranged from 45% (hospital number 10) to 3% (hospital number 6). The mean, median and SD were 28%, 30% and 11%. Treatment with up to three antibacterials ranged from 0% (in hospitals 6 and 19) to 8.1% (hospital number 17). In this group mean, median and SD were 3.5%, 3 % and 2%. Treatment with up to 4 and 5 antibacterials ranged from 4% (hospital number 3) to 0% in 12 hospitals. Mean median and SD were 0.5%, 0% and 1%. Overall, each patient in the PPS received a mean of 1.4 antibacterials, which varied from 1.03 (hospital number 6) to 1.6 (hospital number 10), with a median and SD of 1.3 and 0.15 (Table A.7.3.12).

Table A.7.3.12: Number of patients received one or more antibacterials and average number antibacterial per treated patients in each hospital and in total

Hospital number	Incidence of multiple antibacterial prescribing per patient % (no.)					Average antibacterials per patient		
	1	2	3	4&5	Patients	Antibacterials	Patients	Ratio
1	81.5 (75)	17.4 (16)	1.1 (1)	0.0 (0)	92	108	91	1.2
2	61.1 (77)	34.9 (44)	2.4 (3)	1.6 (2)	126	170	121	1.4
3	57.3 (43)	33.3 (25)	5.3 (4)	4.0 (3)	75	100	68	1.5
4	76.1 (108)	21.8 (31)	2.1 (3)	0.0 (0)	142	173	139	1.2
5	80.7 (88)	18.3 (20)	0.9 (1)	0.0 (0)	109	129	108	1.2
6	96.9 (95)	3.1 (3)	0.0 (0)	0.0 (0)	98	101	98	1.0
7	63.5 (47)	32.4 (24)	4.1 (3)	0.0 (0)	74	98	71	1.4
8	58.1 (108)	34.9 (65)	7.0 (13)	0.0 (0)	186	251	173	1.5
9	80.0 (144)	18.3 (33)	1.7 (3)	0.0 (0)	180	213	177	1.2
10	47.1 (128)	45.2 (123)	7.4 (20)	0.4 (1)	272	395	251	1.6
11	66.8 (181)	27.7 (75)	4.4 (12)	1.1 (3)	271	346	256	1.4
14	57.0 (159)	36.9 (103)	6.1 (17)	0.0 (0)	279	382	262	1.5
15	66.8 (169)	31.2 (79)	2.0 (5)	0.0 (0)	253	332	248	1.3
16	72.1 (31)	25.6 (11)	2.3 (1)	0.0 (0)	43	54	42	1.3
17	49.0 (103)	42.4 (89)	8.1 (17)	0.5 (1)	210	299	192	1.6
18	67.3 (345)	28.7 (147)	3.7 (19)	0.4 (2)	513	660	492	1.3
19	84.7 (94)	15.3 (17)	0.0 (0)	0.0 (0)	111	128	111	1.2
20	57.3 (157)	38.3 (105)	4.0 (11)	0.4 (1)	274	379	262	1.4
21	61.5 (147)	31.8 (76)	5.4 (13)	1.3 (3)	239	315	223	1.4
22	82.8 (82)	16.2 (16)	1.0 (1)	0.0 (0)	99	115	98	1.2
Total	65.3% (2,381)	30.2% (1,102)	4.0% (147)	0.4% (16)	3646	4,748	3483	1.4
Mean	64.8%	27.7%	3.4%	0.5%				1.33
SD	13.1%	11%	2%	1%				0.15

7.3.11 Use of selected antibacterial groups

The prescription of parenteral antibacterials and the sum of Fluoroquinolones and third generation Cephalosporins were analysed for each of the hospitals (Figures A.7.3.7 and A.7.3.8). Fluoroquinolones and third generation Cephalosporins were selected for examination as they are broad-spectrum antibacterials and available in all of the study hospitals. From a total of 4,748 antibacterial therapies, 1,015 (21.4%) were either Fluoroquinolones or third generation Cephalosporins. The percentage of antibacterial prescribing due to these 2 groups of antibacterials ranged from 9.3% in hospital number 9 to 36.4% in hospital number 5 (mean 20.5%, SD 6.9%). The standard deviation of the mean indicates that there is considerable variation among the hospitals. In 10 hospitals the prevalence was >20% and in 2 hospitals it was just below 10%. The most striking finding is the difference between two infectious diseases hospitals (5 and 17). In hospital 5 CAI and In hospital 17 HAI were more prevalent. On the survey day, hospital 5 was the highest user of Fluoroquinolones and third generation Cephalosporins while hospital 17 was the lowest one. In total, parenteral antibacterials accounted for 64.5% (3,60/4,748) of all antibacterial use, ranging from 39% in hospital number 8 to 91% in hospital number 22 (mean 64.4%, SD= 16%). In 15 out of 20 hospitals, parenteral therapy accounted for ≥50% of total antibacterial therapy.

Figure A.7.3.7: Use of Fluoroquinolones and third generation Cephalosporins in each hospital, presented as a percentage of total antibacterial therapy

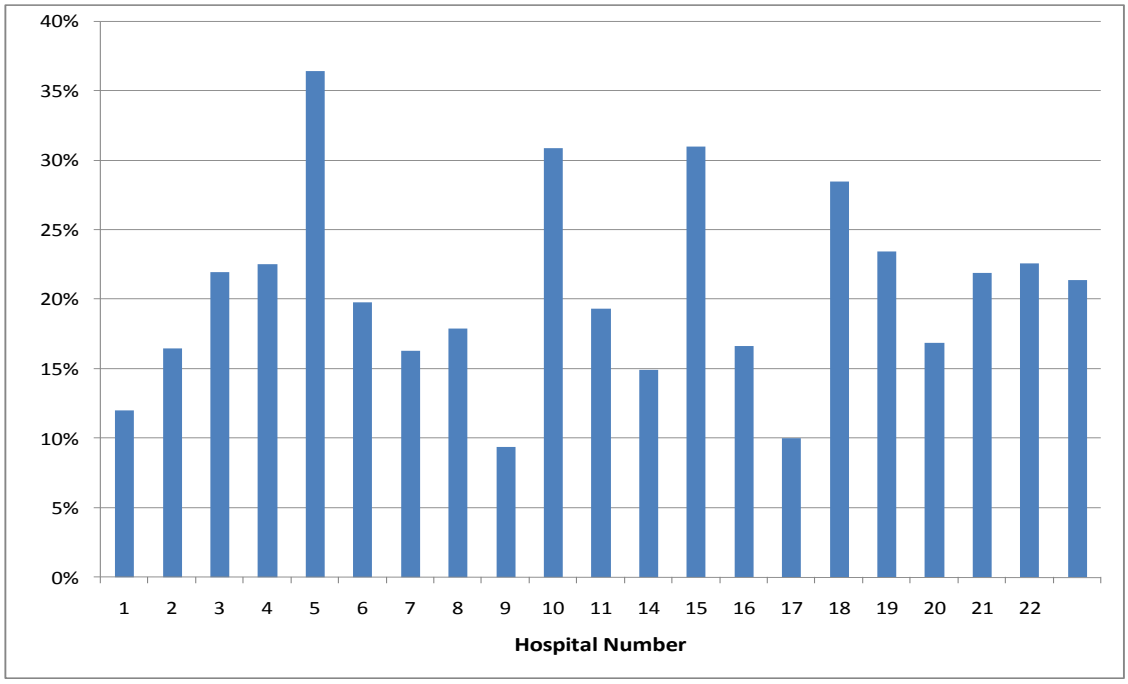
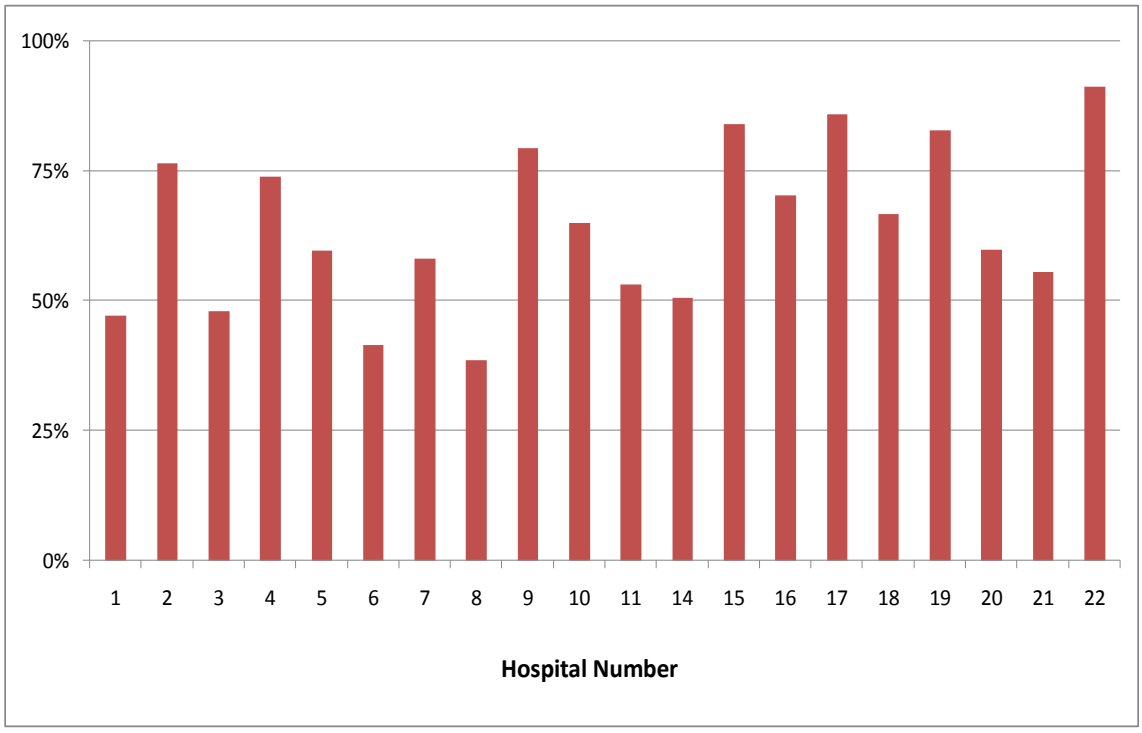


Figure A.7.3.8: Use of parenteral antibacterials in each hospital as a percentage of total antibacterial therapy



7.3.12 Discussion

Presented results for determinants of antibacterial use by clinical groups showed the greatest proportion of antibacterial exposure and use was in medical departments. Across all departments, the PDD/DDD was higher than 1.8. Variation at patient level was most strongly associated with indication and anatomic site. An average PDD/DDD of 2.1 in Paediatric Departments is alarming because the WHO DDD are assigned for adults and the presided daily doses for children are lower. This will need further studies to investigate, especially with regards to absolute number of paediatric ICU beds which was impossible to gauge in this study.

Also analysis of data should be undertaken by breaking children data down into ICU and non-ICU, and into indication and anatomic site as these were beyond this thesis. Nonetheless, in future studies the software should have a warning to avoid entering the survey year as the year of birth. For this study we tried to identify and validate children's data from other inputs which was not impossible for all records.

The most common indication was CAI (47.5%) followed by HAI (28.9%), Surgical prophylaxis (16.8%) and medical prophylaxis. There were differences between CAI and HAI when data were analysed within the hospitals and within anatomic sites of infection. Prevalence of HAI from total admitted patients was 9%.

The prevalence of infection by the number of patients and number of antibiotic therapies for sites of infection revealed that except for the most common sites of infection in HAI (undefined) the other common sites of infection (respiratory, SSTBJ, intra-abdominal, and urinary tract) ranked the same in HAI and CAI, all with higher prevalence in CAI. For different sites of infection, the ranges for DDD/patient and AB/patient in CAI were generally higher in general and the difference was bigger for

each of the anatomic sites. In HAI these two measures have significant positive association therefore in CAI, the use in DDD was higher and it was not dependant on the number of antibacterials used in treatment. The Top antibacterials in CAI and HAI are mainly different for similar sites of infection. The use of Alert Antibiotics was more common in HAI. Only parenteral Metronidazole used both for CA and HA intra-abdominal infections with a PDD/DDD equal to one. Parenteral Amoxicillin & EI was used both in HA and CA respiratory infections but the PDD/DDD was higher in CA and it was the same for oral Ciprofloxacin for SSTBJ in HA and CA. Within the top antibacterials only 4 out of 16 in CAI and 3 out of 16 in HAI have PDD equal to DDD, yet the distribution by anatomic sites are different. Analysis by hospital showed the higher prevalence of CAI (mean 52.2%) and subsequently more use by means of the number of antibacterial treatments and DDD, than HAI. Nonetheless the use by means of AB/patient was higher in HAI (mean of 1.4 versus 1.32 for CAI). Mean PDD/DDD was also higher in HAI (2.2 versus 1.89 in CAI). Without further analysis, which can be necessary, it can be concluded that because CAI is around two times more prevalent although the PDD/DDD is slightly more in HAI the total antibacterial use in hospitals can be better explained by the prevalence of CAI. A preliminary ranking that was performed for 5 measures of antibacterial use (% patients, % AB therapies, % DDD, AB/patient, and PDD/DDD for CAI and HAI suggests applying true ranking. However, it can be assumed that all of these measures are needed to better explain prevalence of antibacterial use. In this study we had two infectious diseases hospital (hospitals 5 and 17). Except for the number of patients receiving antimicrobials from the total number of admitted patients that was high in both of the hospitals (could be expected), they were different in all other measures. Therefore regardless of type of treatment or prophylaxis by anatomic site, it is hard to judge hospitals based on their general characteristics.

The prevalence of taking culture before initiating antibacterial therapy for HAI. In general, most of antibacterials prescribed before taking relevant culture (51%). There were differences based on route of administration and to age groups but the focus was mainly on treatment rather than prophylaxis which showed the start of antibacterials before taking a culture was as high as 44.1% in CAI and 37.5% in HAI. The only anatomic site of infection was urinary tract both for CAI and HAI with a high prevalence of taking culture before treatment (71% and 72%). For other sites of infection, the start of antibiotic treatment without taking a culture was high from 38% to 46% with differences between HAI and CAI. Taking a culture before antibiotic therapy makes it possible to shift to an appropriate choice of antibiotic and it leads to improvement in the antibacterial therapy and a cost saving. Some patients with CAI might have had their culture taken before hospitalisation or they might be on antibiotic treatment on admission. Nonetheless, for two site of infection in hospital acquired, namely, pneumonia and SSTBJ (47.3% and 37.9%) of antibacterials initiated before taking a culture. In daily clinical practice we cannot expect that before all antibacterial therapy a culture test could be taken. On the other hand, in this study prevalence of taking culture before therapy was much higher in UTI than for other sites of infection. It suggests that easy and cheap microbiology tests are more common and traditional. Production of clinically relevant microbiology reports can be an indicator of hospital infection management performance [1, 2] specially for severally ill patients. [3] Patient-specific culture and susceptibility data optimises individual antimicrobial management [4] and improves guidelines for empirical treatment.

The use of third generation Cephalosporins and Fluoroquinolones was as high as 21.4% of the total therapies. This selected group of antibacterials and parenteral antibacterials (which accounted for 64.5% of therapies) are associated with antibacterial resistance and increased cost.

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Appendix A.8: ESAC Hospital Questionnaire

ESAC II, Hospital Subproject

Hospital Questionnaire

Dear colleagues

Within the HC project we wish to identify time trends in antibiotic use in hospitals in an individual basis. This questionnaire is designed to identify any variable that could have an impact on hospital antibiotic.

It is confirmed that in all steps of the project the hospitals' names will be anonymous.

Some questions can be answered simply by a Yes/No and some of them require a brief explanation. Add additional space if required. Please return completed questionnaire no later than 15 April 2006.

A) Population and hospital demographic factors:

Is your hospital a:

1) teaching hospital ? Y/N.....

2) secondary or tertiary? .....

3) Total number of inpatient beds:

2000		2003	
2001		2004	
2002		2005	

4) Number of inpatient deaths:

2000		2003	
2001		2004	
2002		2005	

In your hospital is there

5) an adult ICU?

	Y	N	Number of beds		Y	N	Number of beds
2000				2003			
2001				2004			
2002				2005			

6) a paediatric ICU?

	Y	N	Number of beds		Y	N	Number of beds
2000				2003			
2001				2004			
2002				2005			

7) paediatrics ward(including ICU)?

	Y	N	Number of beds		Y	N	Number of beds
2000				2003			
2001				2004			
2002				2005			

8) haematology speciality?

	Y	N	Number of beds		Y	N	Number of beds
2000				2003			
2001				2004			
2002				2005			

9) an infectious diseases specialty?

	Y	N	Number of beds		Y	N	Number of beds
2000				2003			
2001				2004			
2002				2005			

10) a renal dialysis speciality?

	Y	N	Number of beds		Y	N	Number of beds
2000				2003			
2001				2004			
2002				2005			

11) organ transplant speciality?

	Y	N	Number of beds		Y	N	Number of beds
2000				2003			
2001				2004			
2002				2005			

12) acute beds used for long term care like psychology?

	Y	N	Number of beds		Y	N	Number of beds
2000				2003			
2001				2004			
2002				2005			

13) Number of pharmacists (FTE)?

2000		2003	
2001		2004	
2002		2005	

14) Number of infectious diseases specialists (FTE)?

2000		2003	
2001		2004	
2002		2005	

15) Number of Infection control nurses (FTE)?

2000		2003	
2001		2004	
2002		2005	

16) Number of clinical microbiologists(FTE)?

2000		2003	
2001		2004	
2002		2005	

B- Economic factors:

17) Is drug expenditure in the hospital covered by national health care system?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

18) Do inpatients pay for a proportion of their drug expenses?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

19) Are there financial incentives for the physicians based on their prescribing?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

Within your hospital

20) is the drug budget accounted to clinical speciality?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

21) is the drug budget accounted to hospital pharmacy?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

C- Database factors:

22) Are all antibiotics needed for inpatients supplied only by the hospital pharmacy?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

23) Are antibiotics prescribed at discharge excluded from database?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

24) Are antibiotics supplied to outpatient clinics excluded from database?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

25) Are wasted drugs (e.g. expired in ward stock, damaged, missed, unused liquid preparations) excluded from database?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

26) Are returned drugs to the pharmacy subtracted from pharmacy dispensing data?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

27) Is there occasional drug shortage? Please specify which drugs and in which month or quarter? (This is only relevant to shortage in those antibiotics need to be replaced with antibiotics from a different class or with no substitute at all).

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

28) Which antibiotics were introduced in your hospital during this period? Please specify in which month or quarter.

2000	
2001	
2002	
2003	
2004	
2005	

30) Which antibiotics are no longer available from your hospital pharmacy?

2000	
2001	
2002	
2003	
2004	
2005	

30) If any drug donations are made to/from your hospital, are they considered in pharmacy stock data? Please specify.

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

31) Is there any change in dispensing strategies in your hospital? Please specify.

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

D- Microbiology related factors:

32) Change in policy or facilities in quantity and selection criteria of patients' specimens?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

E- Managerial system factors:

Is there

33) an Infection Control Committee?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

34) an established antibiotic prescribing management group?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

35) local prescription formulary/guidelines on use of antibiotics against diagnosis?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

36) training for medical students/doctors targeted at antibiotic prescribing as a part of their education and/or regular basis?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

37) Are antibiotic policy/guidelines available in printed format?

	Y	N		Y	N
2000			2003		
2001			2004		

2002			2005		

38) Are antibiotic policy/guidelines available electronically?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

39) Is there online decision support system for antibiotic prescribing based on patient specific clinical findings which is used in a routine basis in your hospital?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

40) Are there any restrictions in supply of medicine e.g. a restricted drug procurement list against an approved formulary, stop orders?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

41) Is there regular feedback to physicians on infection control and antibiotic resistance? How often?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

42) Is there regular feedback to physicians on antibiotic use? How often?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

43) Are patients' records, lab results and prescriptions kept in paper or electronic format? (Please provide details)?

	Paper	Electronic		Paper	Electronic
2000			2003		
2001			2004		

2002			2005		

44) Is there any intervention to improve antibiotic prescribing in your hospital? Give details in 1-2 sentences about duration of the intervention and antibiotics included in the intervention.

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		

45) Are there other activities to improve antibiotic prescribing/infection control/hospital cleanness which are regulated by public/NGOs/media rather than by hospital authorities?

	Y	N		Y	N
2000			2003		
2001			2004		
2002			2005		